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VOLUME XLVIII
JULY-DECEMBER, 1943

PUBLISHED MONTHLY
AT MT. ROYAL AND GUILFORD AVENUES, BALTIMORE, MD.
BY THE NATIONAL TUBERCULOSIS ASSOCIATION

Medical
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Medical

JUL 22 1943

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PUBLISHED MONTHLY
at Mount Royal and Guilford Avenues, Baltimore, Md.
by the
National Tuberculosis Association
Business Office, 1790 Broadway, New York, N. Y.

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TYPES OF LUNG DISEASES ENCOUNTERED IN AN ARMY CAMP[1,2]

MORRIS C. THOMAS[3]

Duty in a Station Hospital, serving a camp the size of Fort Knox, offers an experience in pulmonary disease—to say nothing of internal medicine in general—which can be equaled in only a few places. It has been our privilege to see this hospital grow from a 200 bed unit to a 2,000 bed institution. The physical types of patients admitted during this period have passed through a widening sphere and range.

Two years ago, the patients were all Regulars; men making the Army a career; men who chose to be in the service. These soldiers were seasoned troops, well trained and physically capable of standing up under any field conditions.

The early part of 1941 saw the first of the selectee group arriving in definite numbers and increasing in force as the year passed. These men were the pick of the country—men in their twenties, rather carefully selected for physical and mental perfection at the induction centres. They adapted quite easily to Army life and became qualified soldiers in a short time.

The declaration of war brought in a new type of selectee. The increased demand for man-power made necessary the induction of men in the upper age groups. These men were examined just as carefully, but defects were missed which only stress of training could uncover. This group brought in the chronic and degenerative types of disease inherent to early middle age, and presented the physical inadequacies incident to more sedentary living.

The Army camp life levels all individuals to a common plane. They all live in the same type of barracks. They eat a well balanced, nourishing diet, the menus for which are the same in all messes of the camp for any particular meal. They are all dressed alike. The drills and training programs for all units are comparable. Everything is uniform except the individual's resistance and reaction to a disease or infection. This, for us, is one of the interesting parts of the hospital service—how a single common disease entity will be manifested in a multitude of symptoms and clinical findings, and varied in severity.

It is the policy of the Army and Medical Department to hospitalize any cases of suspected or obvious disease as promptly as possible and the men are rather encouraged to comply. This serves a double purpose for the Army. It insures the prompt removal of communicable diseases, with the limiting of contact, spread and transmission within the unit. It insures the immediate institution of appropriate therapy with a resulting decrease in the period of hospitalization and loss of time from the training program.

For Medical Department officers, the advantage of starting therapy promptly

[1] Presented at the meeting of the Mississippi Valley Trudeau Society in Chicago, Illinois, September 18, 1942.

[2] Released for publication by the War Department Manuscript Board, which assumes no responsibility, other than censorship, for the contents of this article.

[3] Lieutenant Colonel, Medical Corps, Station Hospital, Fort Knox, Kentucky.

is quite apparent. There is the additional factor of being able to observe diseases under rather ideal conditions in the early stages; in those first few hours that textbooks ignore, or pass over quite briefly; in that phase where civilian patients are being given home remedies by the family before the doctor is called.

Fort Knox is a training centre. Trainees are sent in for eight to fifteen weeks, depending upon the particular duty to be learned, then are sent on to other organizations. This turnover affords us a wealth of clinical material, but precludes any local attempts at statistical evaluation.

Tuberculosis should play but a minor rôle as a postwar Veterans Administration problem. As you all know, every man receives a chest roentgenogram as part of his induction examination, and is, or will be rechecked upon separation from active service. The films of accepted inductees are retained by the Veterans Administration for future use.

The standards for acceptable chest X-ray films are rather rigid. Active and fibroid tuberculosis are cause for rejection. Inductees are rejected if the chest X-ray film shows more than five hilar calcifications, none of which may exceed 1.5 cm. in diameter, or if there are more than ten parenchymal calcifications, the largest not exceeding 1.0 cm. in diameter.

Our cases of definite tuberculosis are few in number, demonstrating that such a rigid standard for induction is productive of results. Statistically, our rate would probably be classed as of no significance.

Tuberculosis cases seen fall mainly into two groups: those with less than three months service and those with over one year. The disease in the first group is usually in an asymptomatic stage and is manifested by small, localized areas of infiltration. The disease in the second group is more advanced and frequently symptomatic. The majority of cases in both groups are found on routine chest X-ray films, taken for varied reasons, rather than because of the presence of suggestive or definite symptoms of activity.

Pleural effusions are encountered quite frequently, associated with some form of pneumonia. Pleurisy with effusion and idiopathic pleural effusions of tuberculous origin are uncommon. The differential diagnosis problem is met in the same manner as in civilian practice.

The question has been raised as to the likelihood of mixing of films in such mass X-raying as is done at the induction centres. We have had two cases only where this may have occurred.

We do not attempt definitive treatment. The tuberculous patients are transferred to Fitzsimons General Hospital or to a Veterans Administration for further observation and treatment and such transfers are effected quite promptly.

There is one group of patients which creates a diagnostic and disposition problem. Chest X-ray films of these men show parenchymal fibrous strands in one or both upper lobes or solitary homogeneous densities in any portion of the lung fields. The roentgenologist's impression is that of tuberculosis. However, clinical and laboratory findings are normal and skin tests with both strengths of PPD are negative. We have tended toward considering these lesions as nontuberculous, but with a little uncertainty as to the exact cause.

Spontaneous pneumothorax is encountered occasionally, none of them has had any serious respiratory embarrassment. Skin tests and stereoscopic chest X-ray films after full reëxpansion determine the disposition. Those showing negative tests and no parenchymal lesions are returned to duty. Some are placed on limited service for follow-up purposes. Pneumothorax due to tuberculosis is cause for transfer to another hospital.

Traumatic pneumothorax would be thought to be a common occurrence in a mechanized unit or post, and particularly in tank crews. Oddly enough, traumatic pneumothorax is rare. Our most severe case was an innocent bystander involved in an automobile accident.

Bronchiectasis is a more common disease than tuberculosis, probably because it cannot be diagnosed at the induction centres, except in the well advanced stages, as easily or accurately as can tuberculosis. About one-fourth are admitted to the hospital because of suggestive symptoms. The others are suspected from routine X-ray films, usually because of slow convalescence from a respiratory infection or from a supposed pneumonia. The past histories of these men are uninforming, certainly so far as commonly accepted causative diseases are concerned.

These men have been able to follow some occupation in civil life. Interrogation will disclose that many have selected the particular occupation by necessity, adapting themselves to their physical abilities. They have learned to protect themselves from colds and exposure. Their economic status, or lack of hospital facilities, may have precluded accurate study. The Army training program subjects them to strains and exposure which they cannot evade. The age group encountered in the Army is that in which bronchiectasis may be considered a more benign disease, before repeated infections has produced marked fibrotic changes. Those with obvious disease are eliminated at induction.

The complaints elicited from these patients are minor in character for the majority of the group. Cough is usually negligible or absent. Expectoration is absent or consists of a small amount raised in the early morning. Very few complain of even transient foul sputum. There may be a history of occasional chest colds which persisted longer than the average. Changes in the finger tips and nails are rarely seen. In fact, we do not expect to secure a so-called classical history or group of physical findings.

The bronchograms obtained after lipiodol instillations show bronchial changes running the gamut of pathology, varying from minor cylindrical and saccular changes, to massive involvement of both lower lobes. There is little correlation between the clinical symptoms and the radiographic findings.

Since the symptoms are unreliable and may be misleading, we have adopted the policy of doing lipiodol instillations on all men who show abnormal basal markings, shifting of the heart or delayed resolution of a pneumonia. Our percentage of positive findings certainly justifies our efforts. Since our percentage of proved cases is so good through selecting cases by the above standards, we wonder how many other asymptomatic cases we are missing.

Bronchial asthmatics are inducted for a definite reason. The man must be

seen in a definite attack; his word alone cannot be accepted. There is the constant problem of attempts to evade military service and claimed asthma is a frequent excuse. The frequency and severity of the attacks regulate somewhat the disposition made.

Haemoptysis may be due to a pulmonary lesion and it may be faked. The complaint of coughing of blood can test the patience and diagnostic acumen of the best. We cannot risk returning the man to duty or claim malingering until we have exhausted every form of investigation. We have learned that a malingerer doesn't relish a second bronchoscopy.

Pulmonary malignancies have been encountered in this younger age group. Two were carcinomata, one a sarcoma and one was a pulmonary manifestation of a generalized lymphoblastic sarcoma.

Cysts of the lung are oddities. The majority are probably eliminated at the induction centres. The same may be said of the dust diseases.

Rheumatic involvement of the lungs has been encountered in 3 individuals, the diagnosis being made by elimination. All 3 of these affected the left lower lobe and accompanied a pericarditis and endocarditis. These cases were admitted as pneumonias. The exact nature was first suspected from the slow resolution of the pneumonia, or from cardiac murmurs, supported by electrocardiographic changes and diagnosed finally by the subsequent course.

Influenza has occurred in only one epidemic, in December of 1940. This outbreak was violent, but short-lived. No pulmonary complications were encountered.

Pneumonias account for the largest group of major pulmonary infections. The number in the hospital shows a seasonal variation, as expected, reaching a peak in March and April. We have had 2 deaths in two years.

We have seen pneumonias go through many cycles, each varying in some or many ways from prior cycles. Each group may resemble prior forms of the disease in some manners, but no two have been identical.

Pneumococcic pneumonia forms a small group only of our pneumonia patients. The onset and course of the disease is rather constant and no difference has been noted from cases occurring in the same age group in civil practice.

One variation from an accepted standard of diagnosis has been observed. Our patients are admitted within a few hours after the initial symptoms. They show varying degrees of cyanosis, cough, rusty sputum, chest pain and dyspnoea. The area of infection can be outlined by physical examination. The white blood count is elevated and typable pneumococci can be found in the sputum. Initial chest X-ray films, however, may show no evidence of haziness or consolidation. Serial X-ray films after institution of sulphonamide therapy may fail to show any further evidence of disease or, at the most, only a small area not having the density usually associated with pneumonic consolidation.

About the first of February, 1941, we began to encounter a new form of pneumonia. The onset was slower, with prodromal symptoms extending over one to five days. These men would return shortly after discharge from the hospital or would suddenly develop their pneumonia while convalescing from other

diseases or operations. Others would be admitted as nasopharyngitis and develop their disease one to five days later. Still others would be admitted with clinical disease.

The symptoms were out of proportion to the physical and radiological findings. The cough was harassing and nonproductive. Substernal rather than pleural pain was noted. The fever would range from 100° to 103°F. Initial blood counts averaged around 15,000 white cells. The physical findings of changes in breath sounds and râles varied from absent to diffuse throughout the chest. It was noticed quite early that there was no correlation between the physical findings and the X-ray findings, either as to location or extent of involvement. X-ray films showed a patchy, lobular type of consolidation, usually confined to one lobe, and the right middle lobe in particular. The finding on the initial chest X-ray film was considered adequate evidence that pneumococci would not be present in the sputum. Areas of decreased density, suggesting cavitation, were seen. Serial X-ray films of some would show clearing of the initial areas, with new consolidations in other lobes. Pneumococci could not be demonstrated on smear or culture.

The laboratory officer was condemned for his failure to demonstrate a specific organism. The admission of an increasing number of these cases proved that we were dealing with a new form of disease. We called it, first, bronchopneumonia, or referred to it as virus pneumonia, Fort Knox pneumonia, or the "pip," all for lack of a better name.

Later in the spring, another form of pneumonia appeared rather suddenly. These men were quite ill, and the symptoms severe. White blood counts averaged above 25,000. Pneumococci, frequently nontypable, could be demonstrated in the sputum of about half of this group. An outstanding symptom was the expectoration of frank blood. X-ray films showed more extensive involvement, lobar in distribution, but still not the solid density of complete consolidation. This phase lasted but a short time.

The cases admitted during the summer of 1941 resembled those seen in the initial form.

A change in the X-ray appearance of the pneumonias was observed in the late fall of 1941, and this form has remained rather constant to date. These films showed homogeneous areas of decreased density occupying part of a lobe. Discernible in this general density were small rounded areas of greater opacity.

The symptoms, clinical and laboratory findings in this group have been about as varied as the cases themselves. Attempts to formulate some definite criteria for classification have been only partially successful. Constant review and revision of standards of diagnosis have clarified most of the group, but some still remain in an undetermined group.

The symptoms are varied from none to severe. Chest X-ray films of some soldiers, taken for routine purposes, have shown extensive areas of involvement. These men were performing full duty and objected quite strenuously to being hospitalized when they felt perfectly well.

As would be expected, symptoms were present in the majority. Outstanding

was an initial harsh, nonproductive cough, rather resistant to ordinary therapy. Sputum, when produced, was mucoid and blood tinged. Some patients raised profuse quantities of clear, thin mucus. Sore throat, headache and anorexia were frequent complaints. Cyanosis was absent or only faintly perceptible. Fever was not observed in some cases, but the majority showed an admission fever of 102° to 104°F. The fever dropped promptly for the most part, but might continue for two to five days. The pulse rate followed the fever curve. Respirations were normal. Chest pain was common, pleurisy uncommon. Râles were usually present. Blood counts on admission showed normal leucocytes or a mild leucocytosis, not exceeding 15,000.

Chest X-ray films showed no correlation between the clinical picture and the extent of the infection in the lungs. Hilar shadows were increased in size and density in all cases. Parenchymal lesions varied from slight mottling to extensive involvement. There was a tendency for new lesions to appear as older areas cleared. Time of resolution was unpredictable; some cases showed prompt clearing; others required weeks to return to normal.

The diagnostic questions which this group may raise are many and have been thoroughly discussed by our staff. Is this a new disease? It does seem probable in many ways. Is it merely a severe form of bronchitis, the parenchymal involvement being discovered only because X-ray facilities are available? If so, then the number of cases found should be much higher. If the blood counts are used as criteria, two groups can be developed. The cases showing an initial leucocytosis may be classed as bacterial in origin and related to some type of bronchopneumonia. Those showing normal leucocyte counts may be grouped with the atypical or virus pneumonias. Such a differentiation cannot be made clinically.

These forms of pneumonia have been reported officially as bronchopneumonia, atypical pneumonia or pneumonia unclassified. Terminology to describe this condition adequately has not been approved. We are frank to admit that we do not know what this form of pneumonia is, or how it should be classified. A causative organism has not been demonstrated and the aetiology is a matter of conjecture. None of our patients has died, so the pathological changes present are unknown. The rapid change observed in the lesions would tend to support bronchiolar or bronchial occulsion as one factor, rather than actual consolidation.

A new form of pneumonia has appeared in the past few months to which we are applying, perhaps correctly, the term of atypical pneumonia. The onset is rather sudden and accompanied by extreme prostration. The cough is harassing and cannot be controlled by large doses of codeine. The sputum is blood-tinged to frank blood. There is severe retrosternal pain and sense of opression. Cyanosis is marked, persistent and only partially relieved by oxygen. Râles are present through most of the lung fields. A constant finding is that of white blood cell count below 8,000. Counts of 3,000 have been observed. The severity of the infection is proportional to the degree of leukopenia. The increase in temperature, pulse and respiration are consistent with the severity. Here

again, the extent of the involvement as demonstrated by X-ray is not correlated with the clinical observations and severity of the infection. Convalescence is rather slow. A constant finding is a leucocytosis during the early convalescent period. These cases, unlike other pneumonias, have shown absolutely no response to chemotherapy. The virulence of the disease seems to be increasing.

SUMMARY

1. A brief résumé of the types of lung diseases encountered in an Army camp has been presented. In general, soldiers are subject to the same diseases they would encounter in civilian life, and the cases seen in the hospital are essentially of the same types anticipated in a comparable age group in civilian practice.

2. Prompt hospitalization of the sick permits the study and observation of the early manifestations of many diseases. It has demonstrated that the accepted early symptoms of some diseases are not "early." It has shown definitely that symptoms may be misleading and may be inconsistent with the clinical findings; that serious disease may produce only trivial subjective symptoms.

3. Hospital facilities are such that obscure or chronic diseases can be given the detailed and special examinations required for accurate diagnosis.

4. Observation of diseases under such controlled conditions emphasizes the fact that the clinical findings present in a given disease entity are neither fixed nor constant, but are altered and varied by the individual's reaction to his infection.

SUMARIO

1. Preséntase un breve resumen de los tipos de neumonopatías observados en un campamento militar. En general, los soldados padecen de las mismas dolencias que se encuentran en la vida civil, y los casos observados en el hospital corresponden en el fondo a los mismos tipos que son de esperar en un grupo de edad comparable, en la práctica civil.

2. La rápida hospitalización de los enfermos permite estudiar las manifestaciones incipientes de muchas enfermedades, habiéndose observado que los síntomas tempranos aceptados de algunas de ellas, no son realmente "tempranos." Se ha demostrado también, definitivamente, que los síntomas pueden dar origen a errores y no conformarse a los hallazgos clínicos; y que una afección grave puede producir síntomas subjetivos puramente triviales.

3. Los recursos hospitalarios disponibles son de tal índole, que las enfermedades obscuras o crónicas pueden ser objeto de los exámenes minuciosos y especiales que exige el diagnóstico exacto.

4. La observación de las enfermedades en condiciones tan comprobadas pone de relieve el hecho de que los hallazgos clínicos presentes en una entidad patológica dada no son ni fijos ni constantes, sino que los altera y varía la reacción del individuo a la infección de que padece.

BRONCHIECTASIS SECONDARY TO PULMONARY TUBERCULOSIS[1]

ARNOLD B. RILANCE AND BRUNO GERSTL

Bronchiectasis, secondary to tuberculosis, has been regarded by most clinicians and pathologists as a relatively benign complication, warranting but little consideration. This attitude is supported by the fact that at autopsy a high proportion of all cases of tuberculosis show some evidence of bronchiectasis, yet in relatively few does the bronchiectasis appear to play any recognizable part in the picture of the tuberculous disease. Though this be true, it is our belief that, in a small proportion of cases, bronchiectasis assumes a place of major importance in the evolution of the pulmonary lesion and the development of the terminal pathological condition.

MATERIAL STUDIED

This report is concerned with a series of 47 tuberculous patients, in whom bronchiectasis, demonstrated during life by bronchography or found at autopsy, was believed to play such a rôle. In 12 patients the bronchiectasis was found at autopsy. In them, unusual degrees of bronchial dilatation were demonstrated and, though unsuspected during life in the majority of instances, the bronchiectasis was felt to be of more than the usual significance.

The remaining 35 cases were studied with lipiodol while undergoing treatment in the sanatorium, and the information available about them was purely clinical in nature. In them, certain symptoms had been noted which suggested the possibility that more than the usual amount of bronchiectasis was present and that this bronchiectasis was the cause of the significant symptoms the patients presented.

Of the latter group of 35 cases, in 3 the bronchiectasis was felt to be independent of the tuberculous process and merely accidentally associated. The bronchiectasis was confined to the basilar portions of one or both lungs in each case, with what appeared to be typical tuberculous infiltration in one or the other apex. The sputum of 2 of these cases showed tubercle bacilli for a short time during the active phase of the apical lesion. Bronchiectasis of the upper lobes was ruled out by bronchography. Typical foul sputum with clubbing of the fingers had been noted for many years, long before any evidence of tuberculous infection was to be found.

In the remaining 32 cases, the bronchiectasis was believed the result of the tuberculous disease that was present in the lung. Sputum, frequently copious and purulent, was never foul. Marked degrees of clubbing were absent. Lipiodol studies were made and demonstrated the moderate to marked degrees of bronchiectasis present in each case.

[1] From the Laurel Heights State Tuberculosis Sanatorium, Shelton, Connecticut, and the Department of Pathology, School of Medicine, Yale University, New Haven, Connecticut.

In 22 of the latter 32 cases, active tuberculosis with positve sputum was present when the patients were admitted to the sanatorium. In 17 the sputum became negative and X-ray changes showed progressive healing of the disease. Residual sputum in appreciable amounts, however, not infrequently associated with low grade fever or occasional haemoptyses persisted. Moreover, physical signs, particularly coarse râles, continued to be prominent findings on physical examination. Such a sequence of events prompted further investigation including lipiodol study of the bronchial tree, which resulted in the demonstration of significant bronchiectasis, believed to be the source of the remaining symptoms the patients presented. In many of these patients, if the symptoms were to be explained on the basis of the parenchymal tuberculous lesion, one would be forced to conclude that the tuberculous disease was still active, requiring further energetic treatment. Such apparently was not the case. It is of some importance to note that in none of these patients was the possibility of bronchiectasis even suspected on admission to the sanatorium. With the passage of time, the healing of the tuberculous disease as seen by X-ray, and the conversion of the sputum, the bronchiectatic element in the disease assumed a more prominent part in the clinical picture.

In 5 patients, the sputum remained positive in spite of prolonged periods of treatment and what appeared to be adequate healing of disease as seen by X-ray. Bronchoscopy was not available for study of such cases at the time these patients were under observation. Lipiodol studies were made and appreciable degrees of bronchiectasis were demonstrated. It was felt altogether likely that tuberculous involvement of the bronchi in the involved segments of the lung was the probable basis for both the positive sputum and the persistent symptoms, and was the aetiological factor underlying the bronchiectasis itself.

The remaining 10 cases were of particular interest. Suppurative bronchiectasis dominated the picture from the very beginning of the clinical onset of their respiratory disease. The symptoms noted by them, such as fever, night sweats, cough with copious expectoration, haemoptysis, gradual loss of weight and strength, dyspnoea etc., are all symptoms usually attributed to active tuberculosis and were interpreted as such by the referring physician. In contrast to the symptomatic evidence of active pulmonary infection, they failed to show in any other respect evidence of active tuberculosis, either on admission to the sanatorium or over varying periods of observation. Their sputum was consistently negative for tubercle bacilli while under observation, though in one a positive sputum had been reported some time prior to admission. In another, following a long period of exacerbation of bronchiectatic disease, a positive sputum was found for the first time. In them, the tuberculosis had apparently run a very chronic course, failing to produce any noticeable deterioration in health, till a suppurative bronchiectasis forced them to seek medical advice. At this time, X-ray films of the chest showed the typical appearance of chronic fibroid or fibrocavernous tuberculosis. The question of bronchiectasis was raised when, in spite of clinical evidence of active pulmonary tuberculosis or X-ray evidence of cavitation, the sputum was found to be persistently negative

for tubercle bacilli after many examinations. Moreover, the physical signs noted in these cases were suggestive of active progressing tuberculosis, though this seemed inconsistent with the negative sputum findings. The sputum was almost invariably quite copious and mucopurulent in character, containing large numbers of many types of pyogenic organisms. Because of the lack of any preceding history of definite tuberculosis, it was impossible in these cases to say when the tuberculous element of the disease became inactive, and when suppurative bronchiectasis had its onset. It was in this group that some cases of the most marked bronchiectasis were found. That the bronchiectasis was secondary to a preceding tuberculosis was not absolutely proved in each case, though from the X-ray appearance of the disease and the appearance of the bronchi after lipiodol instillation this seemed to be certain. In not a few, cavitation was visible by X-ray in the upper lobes, and only after further study was the basis of this cavitation demonstrated to be a secondary bronchiectasis.

The justification for ascribing these patient's symptoms and disability to bronchiectasis, rather than to active tuberculosis, would seem to lie in the following facts. In spite of evidence of marked clinical activity of disease, a repeatedly negative sputum was found. Secondly the plain serial X-ray films failed to show any significant progressive or regressive changes over the period of observation. Improvement in all instances, except one, was of a clinical nature, unassociated with the roentgenographic changes usually found in regressing tuberculosis. It is of importance to note that, in this group, the patients all presented themselves for the first time to their physician with the clinical picture of disabling pulmonary disease which, on superficial observation, would unquestionably be interpreted as obvious evidence of active tuberculosis. The significant point illustrated is that bronchiectasis in tuberculous persons may in some instances so closely simulate active tuberculosis as to be very readily confused with it unless the other possibility is in mind. The significance of tuberculous bronchiectasis may further be judged to some extent by the fact that 5 of the 47 patients died as a result of the bronchial suppuration or the complications thereof. Three who came to autopsy had nontuberculous abscesses, one in the brain, one in the liver and one in the kidney. Two others died due to suppuration developing distal to a tuberculous bronchostenosis.

ROENTGENOGRAPHIC FINDINGS

With the increased use of bronchography in the study of chronic pulmonary disease, it has become recognized that many unusual and atypical types of bronchiectasis are found. It would be of some importance to determine those characteristics of tuberculous bronchiectasis that would help in the differentiation. The roentgenograms of all the patients have been reviewed with this in mind.

The general appearance of the plain roentgenogram failed with but rare exceptions to demonstrate anything that might be considered unusual in ordinary chronic tuberculosis. If any abnormal shadows were produced by the bronchiectatic process, they had been completely masked by the tuberculous process

which was present. Following the instillation of lipiodol, certain diffuse changes in the pattern of the bronchial tree were noted frequently. A moderate to marked degree of distortion and abnormal angulation of the bronchi was found in over one-half of the cases. The appearance suggested that the bronchi were being irregularly displaced out of the normal position by the pulmonary fibrosis in their vicinity.

Relatively normal, as well as ectatic bronchi, were frequently affected in this way.

In 25 instances, the location of the bronchiectasis and the area of major tuberculous involvement coincided. In 7, however, the bronchiectasis was located in the least diseased portion of the lung or in areas apparently free of tuberculous involvement. It was extremely frequent to find areas of tuberculous infiltration entirely free from bronchiectasis and bronchiectasis elsewhere in the same patient.

The main differences to be noted between the patterns of tuberculous and nontuberculous bronchiectasis would seem to be that in the former a rather marked degree of distortion of the bronchial tree occurs, quite apart from the ectasia that is present. Second, no close anatomical correlation is found between the location of the pulmonary fibrosis, as seen by X-ray, and the location of underlying bronchiectasis that would explain the fibrosis. In nontuberculous bronchiectasis, on the other hand, gross distortion of the bronchial tree is rarely found, except where atelectasis or some specific fibrosing pulmonary disease is present. Second, there is usually a very close correlation between the location of pulmonary fibrosis and the underlying bronchiectasis as seen by X-ray.

The individual cylindrical and fusiform dilatations showed nothing very unusual. In 12 instances saccular dilatations were noted. They were invariably located in a contracted fibrotic upper lobe. In the plain X-ray film they had the usual appearance of chronic fibrous walled tuberculous cavities, for which they were invariably mistaken. The possibility that these cystic bronchiectatic lesions in the contracted tuberculous upper lobe are in reality reëpithelialized tuberculous cavities will be referred to below. Thin-walled cystic lesions surrounded by well aerated lung parenchyma were neither seen in the plain film nor visualized with the aid of lipiodol in any instance. This is partly accounted for by the fact that certain cases of typical cystic disease of indefinite aetiology and localized to the upper lobe were not included in this series of cases.

INCIDENCE OF BRONCHIECTASIS IN TUBERCULOSIS

In discussing bronchiectasis, secondary to tuberculosis, one might well question what is meant by the term itself. Potter and Pagliughi (1) made lipiodol studies on an unselected series of 180 tuberculous patients and demonstrated bronchiectasis in 45 per cent. Murphy (2) reported finding bronchiectasis in 61 per cent of 65 cases studied with lipiodol. In contrast with these figures is the fact that apparently but a small proportion of such patients ever develop significant symptoms that can be attributed to the underlying bronchiectasis. One is forced to conclude that a benign bronchial dilatation may be found rather

frequently in tuberculous individuals. A much less frequently found clinical type, exemplified in this series, is less benign and apparently slowly progressive, producing the usual symptoms of bronchopulmonary suppuration. Though the term bronchiectasis may be used in the strict sense of the word to apply to both of these types of bronchial dilatation, it should be noted that only the latter type conforms to the usual picture of bronchiectasis as seen in nontuberculous disease of the lung. The underlying difference in the two types may depend not on the degree of bronchial dilatation that is present, but on the amount of functional impairment that is associated with the dilatation. That pulmonary fibrosis may produce a benign compensatory bronchial dilatation in many patients is not an unreasonable assumption. On the other hand it may not be assumed that significant impairment of bronchial function necessarily results from this dilatation. Other factors, such as direct invasion of the bronchial wall by tuberculous or other specific infectious processes, may be necessary before function will be so impaired as to precipitate the development of suppurative bronchiectasis. This is to some extent supported by the fact that suppurative bronchiectasis has not been found, in this series, to develop in arrested cases of tuberculosis unless symptoms of the condition were already present while the patients were under active treatment. If compensatory bronchial dilatation were the important factor in precipitating suppurative bronchiectasis, one would expect the complication to appear with increasing frequency with the passage of time among those patients discharged in apparent good health with well fibrosed lesions. On the contrary, suppurative bronchiectasis seems to appear with greatest frequency in some cases of active tuberculosis during the evolution of the active disease.

MECHANISM OF DEVELOPMENT OF LESIONS

Certain suggestions as to the mechanism of the development of bronchiectasis secondary to tuberculosis have been made in the past (3). Lemoine (4) reports 4 cases of tuberculosis with secondary bronchiectasis in which he believes occlusion of the bronchial arteries could be demonstrated grossly, where the artery was close to either an enlarged tuberculous bronchial lymph node or was involved in the peribronchial fibrosis resulting from a tuberculous lymphadenitis.

Baum and Amberson (5) recently noted the report of Buhl, of instances of bronchial dilatation resulting from secondary pyogenic organisms invading the bronchial wall apparently through the site of a tuberculous ulcer in the bronchial mucosa. Another type of localized tuberculous involvement of the bronchus that predisposes to the development of suppurative bronchiectasis is tuberculous bronchostenosis.

Whatever the actual mechanisms involved in the development of suppurative bronchiectasis in tuberculous patients, it seems altogether likely that it represents a specific pathological process due to tuberculosis directly involving certain segments of the bronchial tree and is something quite different from the benign dilatation that might be explained on the basis of pulmonary fibrosis. Once having developed, secondary changes due to the presence of pyogenic bacteria may determine the severity and the course the condition is to follow.

CASE REPORTS

Case 1: S. S., white male, age fifty-one, originally admitted to Laurel Heights on February 3, 1933, where he remained till discharge August 29, 1937.

In 1916, at the age of thirty-four, the patient had an haemoptysis. A diagnosis of pulmonary tuberculosis was made and observation at a sanatorium for three months followed. At that time tubercle bacilli were present in the sputum. The disease was felt to involve the whole right lung and the left upper lobe. There were no physical signs suggestive of cavitation and X-ray examination failed to demonstrate such or any area suggestive of cystic disease in the right upper lobe. The patient soon returned to work and apparently remained well, though slight cough and expectoration persisted till

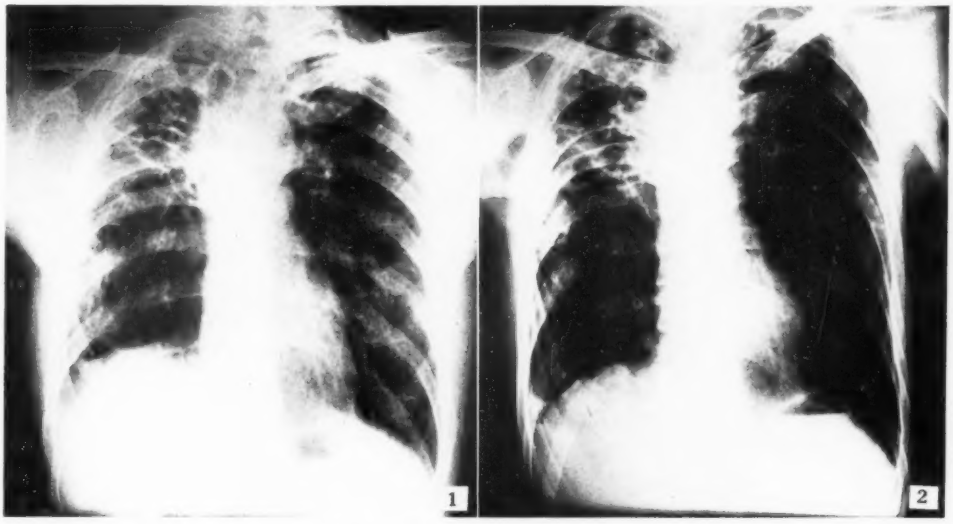


FIG. 1. Case 1. On admission February 3, 1933. Note multiple "honeycomb" cavities in right upper lobe. Note thin-walled cavity in second interspace which was found at autopsy to be in the middle lobe.

FIG. 2. Case 1. Readmission November 17, 1941. No essential change over period of eight years.

1932 when pleurisy developed. No information is available as to the presence or absence of tubercle bacilli in the sputum during this interval of sixteen years.

On admission to Laurel Heights in 1933, the patient was somewhat undernourished but otherwise in good general condition. The sputum was positive. The X-ray film (figure 1) showed numerous honeycomb-type cavities involving the right lung down to to the level of the second rib anteriorly. Below this well demarcated area there was some soft infiltration in the centre of which a cavity was located. During the next four and one-half years the sputum remained intermittently positive, though his general condition continued to be satisfactory. The honeycombed upper lobe lesion showed no change. The more recent lesions in the middle third showed some instability with a small cavity appearing and then disappearing, only to return in the same place at a later date. Phrenic paralysis was ineffectual. The patient was discharged to his home in August, 1937 as quiescent with positive sputum. On November 14, 1941 the patient was read-

mitted suffering from carcinoma of the stomach and died on December 3, 1941. An X-ray film at this time (figure 2) showed no change from the status found at discharge in 1937.

Autopsy findings: At autopsy a scirrhous carcinoma of the pylorus of the stomach was found with extensive carcinoma, seeding the visceral and parietal peritoneum. Two thousand cc. of free fluid were present in the abdominal cavity.

Numerous fibrous pleural adhesions were noted on the left side, leaving several patent compartments in the pleural cavity, while the right pleural space was completely obliterated by fibrous adhesions. A 1 cm. apical cavity was found on section of the left lung surrounded by a firm fibrous wall and containing a small amount of caseous material. A few small nodules with necrotic centres, well defined by fibrous tissue, were distributed irregularly over the cut-surface of the upper as well as the lower left lobe.

The upper lobe of the right lung (figure 3) was contracted and on section it was found to be composed of many communicating cavities. The shrunken middle lobe consisted of a wedge-shaped area containing several ragged walled cavities. The lower lobe (figure 4) approached normal size. There were two sharply outlined areas of caseation in direct communication with major bronchi and surrounded by a dense fibrous wall. Emphysema was the only other significant gross change.

The cavities occupying the apical part of the right upper lobe were lined by a smooth and shiny epithelium; their lumina appeared to be continuous with dilated bronchi. They were separated by fibrous septa and on microscopical examination (figures 5 and 6) they were largely made up of fibrous tissue in which glandular elements, an occasional smooth muscle fibre and a few collapsed alveolar spaces could still be recognized. Several foci of small round cell infiltration were present within the fibrous tissue. Some of the cavity walls were completely lined by cuboidal or columnar epithelium, while others showed a nonspecific granulation tissue which was partially covered by a single layer of flat epithelium. The vessels were compressed or distorted, their lumina were narrowed by intimal proliferation and their media in several instances showed hyalinization. Desquamated epithelium and a small amount of polymorphonuclear exudate were seen within the lumina of both the bronchi and of the cavities.

The lower part of the upper lobe and also of the right middle lobe contained several cavities of similar shape and separated from each other by fibrous tissue. Their walls were covered lightly with caseous material. When the latter was removed, a yellow-greenish granulation tissue became visible. Only a small triangular area of relatively uninvolved pulmonary parenchyma was seen subpleurally.

Sections of this area (figure 7) showed cavity walls largely made up of granulation tissue containing both epithelioid and giant cells. Glandular elements, changed to small cyst-like structures or partly replaced by tuberculous granulation tissue, as well as cartilages were still recognizable in parts of the cavity wall.

The caseous masses in the lower lobe cavities (figure 8) were surrounded by tuberculous granulation tissue and outside of this a zone of dense fibrous tissue. Emphysema and a

FIG. 3. Case 1. Right upper and middle lobe

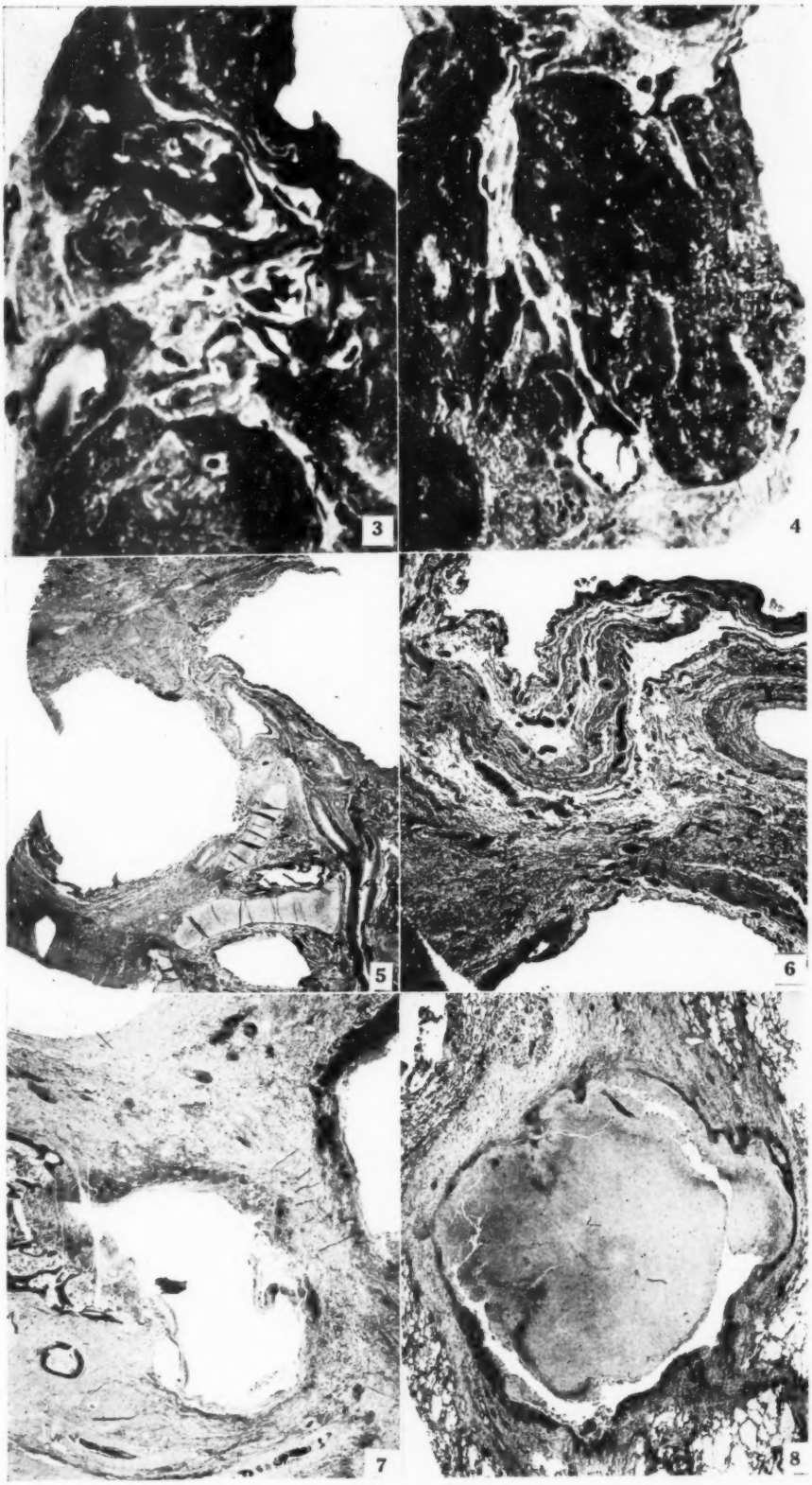
FIG. 4. Case 1. Right Lower lobe

FIG. 5. Case 1. Section taken from wall of upper lobe cavity. H & E ×4.

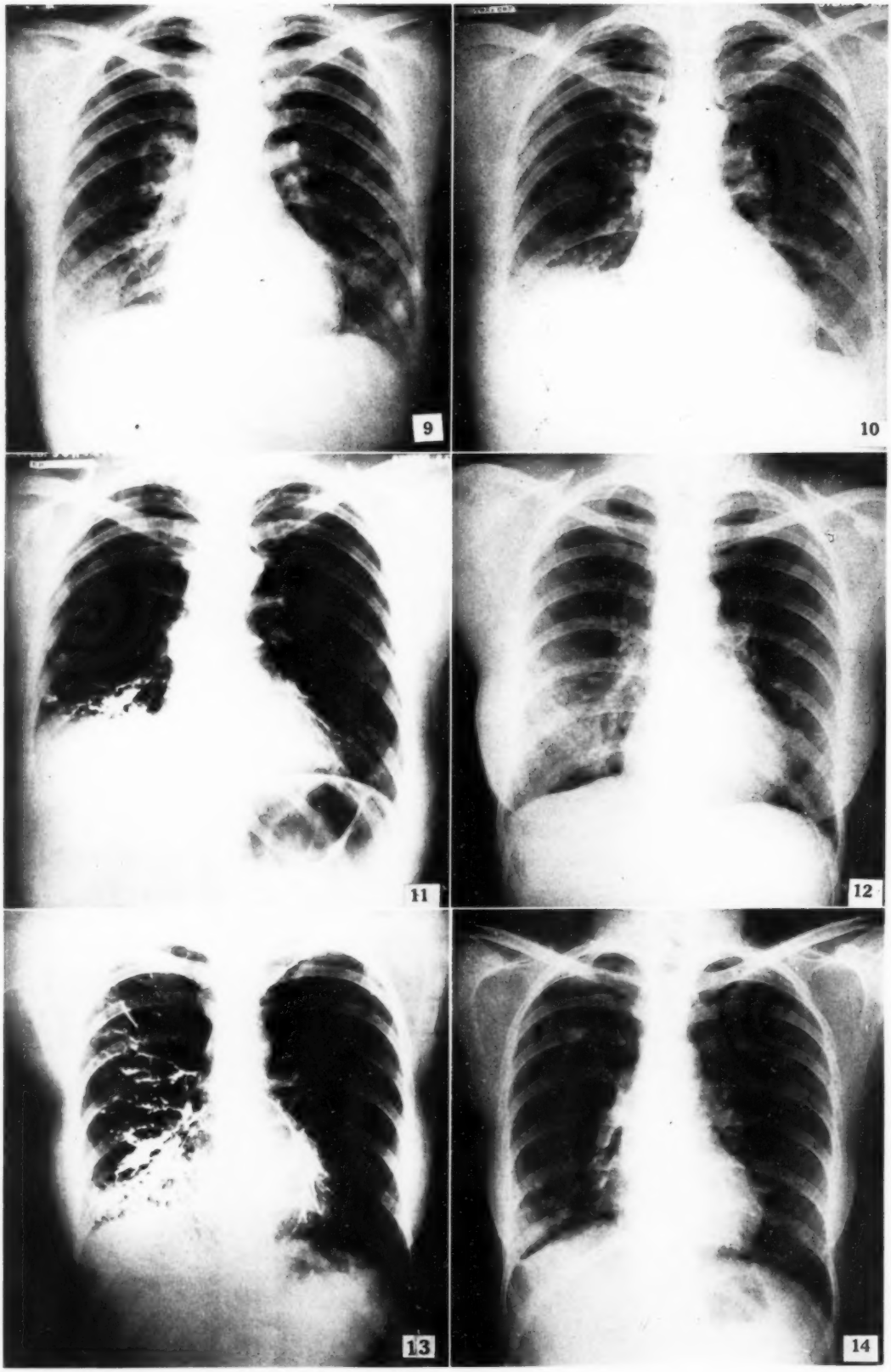
FIG. 6. Case 1. Detail from section illustrated in figure 5. H & E ×18.

FIG. 7. Case 1. Section representing cavity of right middle lobe. Note the partly calcified bronchial cartilage in the wall of cavity. H & E ×5.

FIG. 8. Case 1. Microscopical section of right lower lobe cavity. Note caseous material filling the lumen of cavity. H & E ×4.



FIGS. 3-8



FIGS. 9–14

small amount of interstitial fibrosis were noted in the surrounding lung parenchyma. Some of the alveolar spaces were filled by a polymorphonuclear exudate without morphological evidence of tuberculosis.

The mechanism of the development of the three types of cavities described above may be assumed to be, first, the involvement of the bronchus by tuberculous disease with destruction of all normal bronchial tissue (figure 8); second, the excavation of this granuloma leaving a shaggy walled tuberculous cavity in free communication with the proximal portion of the bronchus (figure 7); third, the reëpithelialization of this excavation leaving a "healed" cavity communicating with the bronchus (figure 5). This mechanism would account for the development of the cystic cavities in the right upper lobe.

Case 2: B. B. In November, 1931, a housewife, age twenty-nine, noticed loss of strength with cough and expectoration. A diagnosis of pulmonary tuberculosis was made.

On admission to Laurel Heights May 11, 1932 her general condition was good. The sputum was highly positive for tubercle bacilli. The X-ray film (figure 9) showed evidence of infiltration throughout the lower half of both lung fields, with a 2.5 cm. cavity at the apex of the right lower lobe.

Artificial pneumothorax was started on the right side in November, 1932 and discontinued as unsatisfactory in August, 1933. A right phrenicectomy was performed on June 11, 1934. From May, 1932 till February, 1936 the patient gained markedly in weight and improved generally. Cough and expectoration were moderate, but sputum remained consistently positive for tubercle bacilli. The X-ray films showed marked clearing and the cavity in the right lung closed (figure 10). Because of the persistence of many coarse râles at the base of the right lung and sputum positive for tubercle bacilli, a lipiodol study was made on February 24, 1936. This showed a moderate degree of typical cylindrical bronchiectasis in the right lower lobe (figure 11). The patient was discharged on November 2, 1936 in excellent general condition, but with a persistently positive sputum after four and one-half years of treatment, in spite of what appeared to be a healed lesion from the X-ray point of view. Though bronchoscopy was not performed to rule out ulceration of the major bronchi, it seems likely that the positive sputum had its origin in the ectatic bronchi demonstrated by lipiodol. The appearance of the residual disease very closely simulated the findings in nontuberculous basal bronchiectasis.

Case 3: H. H. This woman, age nineteen, was a clerk. She was admitted to Laurel Heights on November 19, 1933. The family history was positive for tuberculosis. In 1929, X-ray films of the lungs revealed tuberculous infiltration. She rested at home for one year and then worked for eighteen months till symptoms recurred. In October, 1933, prior to admission, artificial pneumothorax was started on the right side and maintained till December, 1933 when it was abandoned as ineffective.

FIG. 9. Case 2. On admission May 11, 1932

FIG. 10. Case 2. Following three years and nine months treatment. Cavity closed and marked clearing of infiltration.

FIG. 11. Case 2. February 24, 1936. Following instillation of lipiodol. Marked bronchial dilatation partially obscured by elevated hemidiaphragm and right border of heart.

FIG. 12. Case 3. On admission November 19, 1933

FIG. 13. Case 3. Following instillation of lipiodol

FIG. 14. Case 3. At discharge May 13, 1938. Persistently positive sputum. No cavity visualized at any time.

On admission her general condition was fair. The X-ray film (figure 12) showed a soft type of infiltration throughout the lower half of the right lung. No cavity was visible at that time nor at any other time subsequently, as seen in serial X-ray films over a period of four and one-half years. The sputum at first was negative for tubercle bacilli, but turned positive in September, 1934, ten months after admission to the sanatorium. It remained intermittently positive from that time on. There were frequent episodes of low grade fever associated with increased cough and expectoration, especially prominent after upper respiratory infections.

The disease, particularly in the right lung was unusually unstable and a right phrenicectomy was performed on July 15, 1935 and repeated on December 17, 1936. Physical signs in the chest revealed many râles especially below the second rib and fifth spine posteriorly. Definite bronchiectasis involving segments of the right lower lobe was demonstrated with lipiodol (figure 13). The patient was discharged on May 28, 1938, improved but with persistently positive sputum. Figure 14 shows the appearance of the lung at the time of discharge. In spite of five years of treatment and inconsistent though progressive clearing of disease according to X-ray observation, a persistently positive sputum remained. Bronchoscopy was not performed to rule out tuberculous bronchitis. As in the previous case, the finding of gross bronchiectasis in the presence of persistently positive sputum not explained on any other basis, suggested a definite interrelationship.

Case 4: R. A. The patient, a male clerk, age twenty-five, had an attack of dry pleurisy in 1925. This was followed by continuous cough and expectoration. In March, 1928 he consulted a physician who made a diagnosis of pulmonary tuberculosis. He entered a sanatorium on April 6, 1928. Artificial pneumothorax was attempted on the left side soon after admission there. He remained under treatment for a period of five months till his transfer to Laurel Heights on September 7, 1928.

On admission he was well nourished. X-ray films of the chest revealed tuberculous infiltration throughout the upper half of the left lung with multiple cavities. The right lung was essentially normal. His sputum was positive. A left phrenic avulsion was performed on November 1, 1929. By February, 1934, after six years of sanatorium treatment, his disease had become quite stationary. A 6 cm. cavity was present in the apex of the left lung with infiltration extending down to the level of the fourth rib and sixth spine posteriorly. In the right lung a moderate amount of infiltration in the right upper lobe had become well organized, leaving some residual fibrosis.

On February 5, 1934 a three-stage thoracoplasty was started on the left side. The third stage was completed on February 26, 1934. Because of the persistent cavity, a two-stage repeat thoracoplasty was performed, the second stage on April 15, 1935. His sputum converted promptly and has remained consistently negative since May, 1935.

FIG. 15. Case 4. Following repeat thoracoplasty April 15, 1935

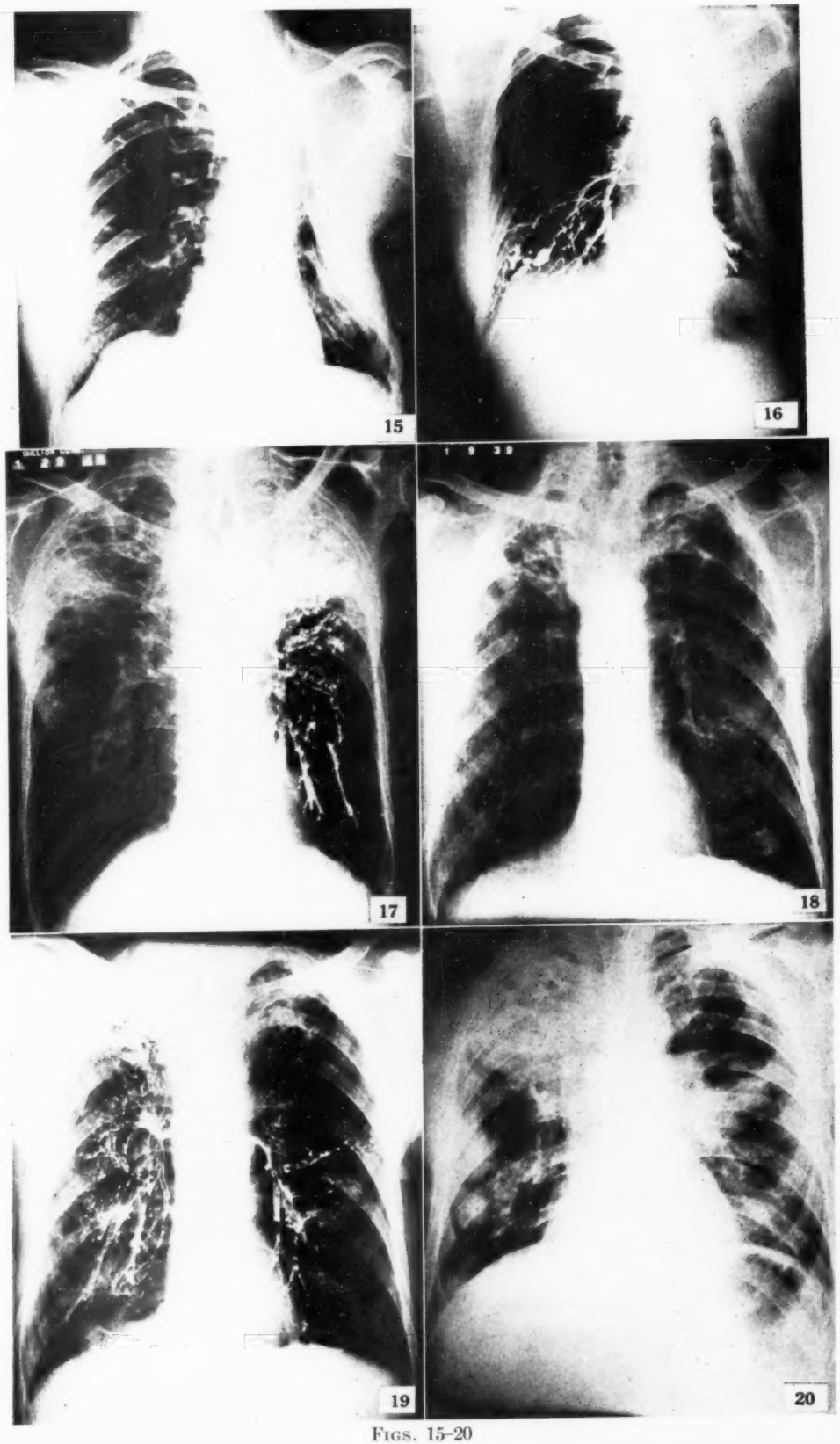
FIG. 16. Case 4. Following instillation of lipiodol July 10, 1936. Bronchiectasis on right confined to middle lobe. Tuberculosis is apparently cured. Residual bronchiectasis causes moderate disability.

FIG. 17. Case 5. Following instillation of lipoidol in left lung. Disease is bilaterally symmetrical in both lungs. Note gross distortion of bronchial tree.

FIG. 18. Case 6. On admission January 7, 1939. Note cavity in right first interspace.

FIG. 19. Case 6. Following instillation of lipiodol. Cavity in first interspace well filled, with fluid level.

FIG. 20. Case 7. X-ray taken June 17, 1940, prior to admission, during episode of pneumonia.



FIGS. 15–20

By March, 1936, in spite of an excellent collapse of the left lung, a persistently negative sputum and a satisfactory general condition, it was noted that he continued to raise from 45 to 60 cc. of mucopurulent sputum each twenty-four hours. Figure 15 shows the X-ray film following thoracoplasty. Bronchiectasis was suspected and a lipiodol study was performed. Figure 16 demonstrates a moderate amount of cylindrical bronchiectasis in the collapsed lower lobe on the left and a moderate amount of bronchiectasis on the right side, demonstrated by lateral films to be in the middle lobe. No evidence of bronchiectasis was to be seen in the right upper lobe. The patient was discharged on June 21, 1937 to his home. During the next four years he was seen periodically. Cough and expectoration continued unabated and following upper respiratory infections this was considerably increased. He had lived a very sedentary life and continued to remain in reasonably good health.

This patient represents a type in whom bronchiectasis was masked by active tuberculosis. Following the healing of his tuberculosis, residual symptoms suggested the possibility of bronchiectasis. It was of interest that the bronchiectasis was found in the left lower and right middle lobes, neither of which had been the seat of extensive chronic tuberculosis.

Case 5: R. S. This patient, a white male of sixty-one years, had an X-ray film of the chest taken in 1936 because of moderate cough and expectoration which had been present for many years. At this time he was told he had inactive pulmonary tuberculosis. Early in 1939, he began to notice anorexia and a gradual loss of 20 lbs. in weight over the next two years. Cough and expectoration increased. Fatigue after ordinary exertion and malaise became noticeable. For three months prior to admission he noticed considerable dyspnoea on exertion which caused him to stop work in August, 1941, and he was admitted to Laurel Heights two and one-half months later on November 13, 1941.

On admission, he appeared markedly undernourished, weak and dyspnoeic. There were frequent days with low grade fever. With the aid of postural drainage, he raised on the average 150 to 200 cc. of mucopurulent sputum every twenty-four hours. It was consistently negative for tubercle bacilli on concentration, though guinea pig inoculation was positive. Sputum cultures revealed a mixture of haemolytic streptococci and non-haemolytic strepto- and staphylococci. Physical signs in the lungs were those of diffuse pulmonary infiltration particularly marked over the upper half of each lung with showers of moist râles and emphysema at the bases.

Sulfathiazole was given with a total dose of 45 g. over a period of nine days. The sputum rapidly subsided and stopped forming entirely by the end of nine days of treatment. He was discharged in February, 1942 having regained 20 lbs. in weight, free of all symptoms except dyspnoea on exertion, and markedly improved in his general health. Figure 17 shows his X-ray film taken following a lipiodol study to demonstrate the bronchiectasis. The lesion seen in the right lung is representative of the type of lesion present in both lungs showing extensive fibrosis and multiple small cavities. The left side after instillation of lipiodol shows the innumerable bronchiectatic and bronchiolectatic cavities present with a moderate degree of cylindrical bronchiectasis in the lower lobe. The dramatic response of this patient to sulfonamide therapy with complete alleviation of his toxaemic symptoms is strong evidence that his disability was due to the bronchial suppuration rather than to active tuberculosis.

Case 6: D. F., white male, age sixty-one, admission January 7, 1939.

In the past fifteen years he had noticed morning cough and expectoration which had

been complicated by frequent chest colds during the latter three years prior to admission. In October, 1938 he developed a chest cold with cough and expectoration, malaise, loss of weight and anorexia, and the same month his sputum was found to be positive for tubercle bacilli by his family physician. He rested at home for three months until his admission to Laurel Heights.

On admission he was obviously undernourished but otherwise in good general condition. Physical signs in the chest were suggestive of cavity in the right upper lobe.

X-ray film of the chest (figure 18) demonstrated a chronic fibroid lesion involving the right lung to the level of the second rib with several areas of translucency most suggestive of cavitation. The sputum was scanty but consistently negative on repeated examination of concentrated specimens. Other laboratory findings were not significant.

X-ray films taken after lipiodol instillation (figure 19) revealed cystic bronchiectatic cavities in the right upper lobe, obviously occupying the same area where cavitation was seen in the plain film. After six weeks observation the patient was discharged. Residual symptoms were felt to be due to the bronchiectasis rather than any activity of the tuberculosis. It is apparent that during periods of reëxacerbation of bronchial infection, patients with this type of disease may develop sputum positive for tubercle bacilli. This disappears rapidly as the acute phase of the infection subsides. The presence of cavitation according to the X-ray film in the face of a negative sputum was the factor suggesting that such cavitation was bronchiectatic, rather than actively tuberculous in nature.

Case 7: G. W., white male, age fifty-eight admission June 28, 1940.

For an indefinite length of time prior to the onset of acute symptoms, the patient had noticed some fatigue on exertion with a gradual loss of 20 lbs. in weight. He stated that in all other respects, however, he was perfectly well till June 6, 1940 at which time he became dizzy and noticed some nausea. He felt feverish and had several chills. That night his temperature rose and he began to cough and raise appreciable amounts of sputum. There was some chest pain. A physician who was called to attend him made a diagnosis of pneumonia. After a week spent in bed at home he entered a general hospital because of the continuation of cough and expectoration with some fever, in spite of adequate treatment. X-ray films of the chest were taken there on June 17, 1940 (figure 20) whereupon a diagnosis was made of "extensive bilateral pulmonary tuberculosis with cavitation." Eleven days after this X-ray examination, the patient was admitted to Laurel Heights. There was daily elevation of temperature to 99.4° and occasionally to 100°F. Sputum was moderate in amount and consistently negative on examination of 7 forty-eight hour specimens. Gastric lavage and guinea pigs inoculated with the treated sediment were negative.

The X-ray film on admission (figure 21) showed several fibrous walled cavities in the shrunken right upper lobe. X-ray films after lipiodol study (figure 22) readily demonstrated numerous bronchiectatic cavities in this area and apparently clearly outlined the obvious cavity seen in the first anterior interspace (figure 20). The remaining bronchi of the lung were considerably distorted and a few cylindrically dilated bronchi were found in the lower lobe.

The original diagnosis of pneumonia in this case seems entirely warranted. The fact that it was superimposed on an unsuspected bronchiectasis secondary to an old tuberculous process was the factor causing confusion early in the course of the patient's illness, leading to the erroneous impression that the patient was suffering from an acute cavitating tuberculosis.

The patient was discharged on September 10, 1940 and was reëxamined on January 17, 1941. At this time his sputum was negative, the X-ray appearance had not changed from the picture as seen at discharge. His general condition was good. It is obvious that if in the future recurrent attacks of pneumonitis should be noted in this area of tuberculous bronchiectasis the casual observer would be inclined to again consider this patient's tuberculosis as active. The possibility must be considered that a chronic disabling phase of suppurative bronchiectasis may develop in this patient at some later date. Sulfonamide therapy though temporary in action might tide him over the more acute episodes in the course of his disease.

FIG. 21. Case 7. On admission June 28, 1940, eleven days after previous film
FIG. 22. Case 7. Following lipiodol instillation, outlining bronchiectatic cavities. Sputum consistently negative throughout.

SUMMARY

Bronchiectasis secondary to tuberculosis has been demonstrated repeatedly to be commonly found in tuberculous patients. Few of these patients, however, exhibit any significant symptoms due to the complication, and it seems likely that, in the majority, bronchiectasis is merely a benign bronchial dilatation not associated with abnormality of bronchial function. A minority appear to develop a true suppurative bronchiectasis that many times, both in severity of symptoms and the resultant disability, overshadows the tuberculous parenchymal disease. It seems justifiable to assume a different aetiological basis for the two types of bronchiectasis.

A series of 47 patients with significant degrees of bronchiectasis in association with tuberculosis has been studied. Twelve patients came to autopsy; 35 were studied by bronchography.

The clinical picture and the appearance of the X-ray films of these patients

have been described, demonstrating the marked similarity that sometimes exists between the clinical manifestations of tuberculous bronchiectasis and those due to active pulmonary tuberculosis. The symptoms of suppurative bronchiectasis secondary to pulmonary tuberculosis may so closely simulate those of active tuberculosis that errors in their differentiation may readily be made. Occasional patients, never cognizant that they have had tuberculosis in the past, may present themselves for the first time, with symptoms due to a suppurative bronchiectasis which may readily be mistaken for active pulmonary tuberculosis.

Suspicion of the presence of tuberculous bronchiectasis should be aroused when patients present the clinical symptoms usually interpreted as evidence of active tuberculosis, in association with either a persistently negative sputum or an X-ray picture which by itself would be interpreted as a healed tuberculous lesion. When all three conditions prevail, the evidence suggesting bronchiectasis is very strong.

Certain characteristics of tuberculous bronchiectasis that appear to differentiate it from the nontuberculous type have been pointed out. Following the instillation of lipiodol into the bronchial tree, gross distortion and abnormal angulation of the bronchi were frequently seen, changes not usually found in cases of nontuberculous bronchiectasis. Cystic bronchiectatic cavities, located in the shrunken upper lobe, appeared to simulate in every respect the usual roentgenographic appearance of chronic tuberculous cavities. The assumption that these bronchiectatic cavities were in reality reëpithelialized tuberculous cavities seems to be supported by the pathological findings reported in one case.

SUMARIO

Se ha demostrado repetidamente que la bronquiectasia, secundaria a la tuberculosis es común en los tuberculosos, pero pocos de esos enfermos manifestaron síntomas significativos debidos a la complicación presente. Parece probable que en la mayoría, la bronquiectasia sea meramente una dilatación bronquial benigna, que no se asocia con anomalías de la función bronquial. La minoría desarrolla aparentemente una verdadera bronquiectasia supurada que muchas veces eclipsa la tuberculosis del parénquima, tanto en la intensidad de los síntomas, como en la incapacidad que produce. Parece, pues, justificado, aceptar una distinta base etiológica para las dos formas de bronquiectasia.

Los autores han estudiado una serie de 47 enfermos en que había una bronquiectasia de importancia asociada con tuberculosis. En doce enfermos se hizo la autopsia, y 35 fueron estudiados con la broncografía.

Descríbense el cuadro clínico y el aspecto de las películas roentgenográficas de estos enfermos, demostrando la decidida semejanza que a veces existe entre las manifestaciones clínicas de la bronquiectasia tuberculosa y las debidas a una tuberculosis pulmonar activa. Los síntomas de la bronquiectasia supurada secundaria a la tuberculosis pulmonar pueden semejar a tal punto los de la tuberculosis activa, que pueden cometerse fácilmente errores al diferenciar los dos estados. De cuando en cuando pueden presentarse por primera vez enfermos que nunca se habían dado cuenta de que tuvieran tuberculosis en el

pasado, y cuyos síntomas se deben a una bronquiectasia supurada que puede confundirse fácilmente con tuberculosis pulmonar activa.

Debe avivar sospechas acerca de la presencia de bronquiectasia tuberculosa, la observación de enfermos cuyos síntomas clínicos suelen interpretarse como síntomas de tuberculosis activa, y están asociados bien con un esputo persistentemente negativo, o un cuadro roentgenográfico que puede a su vez interpretarse como lesión tuberculosa cicatrizada. Cuando existen esas tres condiciones, los datos indicativos de bronquiectasia revisten mucha importancia.

Señálanse aquí ciertas características de la bronquiectasia tuberculosa que aparentemente la diferencian de la no-tuberculosa. Después de estudiar la instilación de lipiodol en el árbol bronquial, obsérvanse frecuentemente desfiguración macroscópica y angulación anormal de los bronquios, que no pueden observarse en los casos de bronquiectasia no tuberculosa. Las cavernas bronquiectáticas quísticas localizadas en el lóbulo superior contraído simulaban en todos los sentidos el habitual aspecto roentgenográfico de las cavernas tuberculosas crónicas. La suposición de que dichas cavernas bronquiectáticas eran en realidad cavernas tuberculosas reepitelializadas parece encontrar apoyo en los hallazgos patológicos correspondientes a un caso.

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CONGENITAL TUBERCULOSIS[1,2]

Tuberculosis Studies in Offspring of Mother Guinea Pigs Heavily Infected Intravenously

H. J. CORPER AND MAURICE L. COHN

One of the best illustrations in medicine of a radical change in view as a result of exact scientific information is that concerning the possibility of acquiring tuberculosis before birth, which was widely believed before this century and with some justification from the evidence at hand. Since then, the possibility of latency of tuberculous infection has again exerted its influence on the conceptions of prenatal infection. To review the theories and conceptions on prenatal infection completely is beyond the scope of this study, since most of these are now incorporated in the more extensive and complete texts on tuberculosis. However, it may be well to point out briefly here that where accurate observations have been possible in birds and cattle the view is held that the disease is a postnatal infection in the majority of cases, although the possibility of egg or transplacental infection is not wholly excluded in massively infected cases. As early as 1894, Bang believed congenital tuberculosis in the calf rare and only possible with wide-spread tuberculosis in the cow or when the uterus is affected. Abattoir experience verifies this. Likewise, visible tuberculosis in guinea pigs and rabbits born of tuberculous mothers is not common if examined shortly after birth or segregated to avoid postnatal infection. The view that human tuberculosis is commonly caused by prenatal infection, championed by Baumgarten, is also not adhered to at present. Mortality statistics in man as well as careful postmortem studies with animal inoculations would not lend support to the prenatal infection theory although it recognizes the possibility in rare cases. One of the earlier theories occasionally expressed by authors, but not subject to proof, was the conception that the fetus or ovum was protected against infection by means of some form of vague immunity which might account for the latency of infection suggested at that time. Within recent years, improved methods as well as more accurately defined quantitative experiments have made possible better definitions of the various reactions resulting in the tuberculous individual. Thus also it has been possible to follow accurately the course of tuberculous disease, especially in the experimental animal, with more refined animal and culture methods. Thus the proof of prenatal infection and prenatal immunity as well as prenatal allergy could be submitted to more accurate test to show their relations and the bearing of these on the tuberculosis problem as a whole. In order to elucidate this problem further, the following experiments were performed on the problem of congenital tuberculosis, prenatal infection and specific tuberculo-immunity and tuberculo-allergy.

[1] From the Research Department, National Jewish Hospital, Denver, Colorado.

[2] This investigation was aided by a gift from Morton May in memory of Florence G. May.

ABSENCE OF CONGENITAL SPECIFIC TUBERCULO-IMMUNITY AND TUBERCULO-ALLERGIC HYPERSENSITIVENESS

In earlier studies it was shown that specific tuberculo-immunity and tuberculo-allergic hypersensitiveness could not be transferred with the blood (1), but this did not exclude the possibility that transfer of these conditions could not occur from mother to offspring *in utero*. In order to ascertain this, a series of female guinea pigs was immunized with 1 mg. of avirulent human tubercle bacilli, using both the subcutaneous and intravenous routes for immunization. This amount

TABLE 1

Absence of congenital specific tuberculo-immunity and tuberculo-allergic hypersensitiveness in the young from vaccinated mother guinea pigs

TREATMENT OF MOTHER AND DAYS AFTER TREATMENT WHEN YOUNG WERE BORN	RESULTS OF TUBERCULIN INTRACUTANEOUS TEST—PPD 2 AND AGE OF YOUNG	AGE OF YOUNG WHEN INFECTED WITH 0.000,1 MG. H 160 SUBCUTANEOUSLY	AMOUNT OF TUBERCULOSIS IN YOUNG 62 DAYS AFTER INFECTION
	days	*days*	
1 mg. avirulent human tubercle bacilli intravenously. 27 days	0—41	50	3*
	0—41	50	3
1 mg. avirulent human tubercle bacilli intravenously. 42 days	0—26	35	4
	0—26	35	4
	0—26	35	4
	0—26	35	4
1 mg. avirulent human tubercle bacilli intravenously. 39 days	0—29	38	3
	0—29	38	4
	0—29	38	3
1 mg. avirulent human tubercle bacilli subcutaneously (in back). 46 days	0—21	30	4
	0—21	30	4
	0—21	30	4
Infection controls			3
			4
			4
			4
			4

* The amount of macroscopical organ tuberculosis is graded from 0 = no visible disease, to 4 = a generalized massive tuberculosis of all the important internal organs.

of avirulent tubercle bacilli also produced a definite tuberculo-allergic hypersensitiveness (2), as well as a definite specific tuberculo-immunity against infection with highly virulent human tubercle bacilli (3), within two to three weeks after the injection of the avirulent bacilli. The young from these females were then tested for tuberculo-allergic hypersensitiveness and for specific tuberculo-immunity. The results are recorded in table 1.

It is evident from the data recorded in table 1 that no appreciable specific tuberculo-immunity, as tested by virulent infection, or tuberculo-allergic hyper-

sensitiveness, as tested by the intracutaneous tuberculin skin test, is transmitted from the vaccinated mother guinea pig to its offspring tested from three to six weeks after birth.

PRESENCE OF TUBERCLE BACILLI IN STILL-BORN AND VIABLE GUINEA PIGS FROM MOTHERS HEAVILY INFECTED INTRAVENOUSLY

In another report (4) it was shown that the offspring of tuberculous mothers as well as mothers given relatively large amounts (1 mg.) of avirulent human tubercle bacilli did not reveal any tuberculo-allergic sensitization. Since tuberculo-allergic sensitization is possible with the parenteral injection of as little as

TABLE 2

Culture findings in still-born and viable guinea pigs obtained from intravenously infected mothers given 0.01 mg. virulent human tubercle bacilli (H160)

DAYS IN UTERO FROM INTRAVENOUS INFECTION TO BIRTH OR EXAMINATION OF OFFSPRING	DAYS AFTER INFECTION WHEN MOTHER GUINEA PIG DIED	VIABLE AND STILL-BORN OFFSPRING		
		Number examined	Age	Culture results‡
			days	
11	11	3	0*	0
12	12	3	0*	0
10	38	2	0†	0
8	15	1	0†	0
12	17	3	0†	0
3	15	1	47	0
8	15	1	5	0
		1	6	0
		1	7	0
9	12	1	3	0
		1	4	0
9	22	1§		

* These guinea pigs were removed from uterus after death of mother.

† These guinea pigs were still-born.

‡ The culture technique used was the oxalic acid digestion-egg-yolk medium method. Corper, H. J., and Uyei, Nao: Additional observations on isolating tubercle bacilli. The oxalic acid reagent for primary culture, Am. J. Clin. Path., 1931, *1*, 135.

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§ Killed at 70 days—3+ tuberculosis.

0.000,001 mg. of avirulent tubercle bacilli (5), the foregoing result would appear to controvert the ready transfer of tubercle bacilli from mother to offspring under ordinary conditions.

To ascertain further the likelihood of passage of virulent human tubercle bacilli to their offspring from heavily infected mother guinea pigs, pregnant guinea pigs were given an intravenous injection (ear vein) of 0.01 mg. of virulent human tubercle bacilli (H160) in fine suspension. The young were studied either by following them at various intervals after viable birth or, if still-born, to submit them to bacteriological analysis. The results of these findings are recorded in table 2.

An examination of table 2 indicates that a relatively large intravenous (0.01 mg.) injection of highly virulent human tubercle bacilli into a pregnant guinea pig does not result in the passage of the bacilli into the offspring up to nine days

FIG. 1

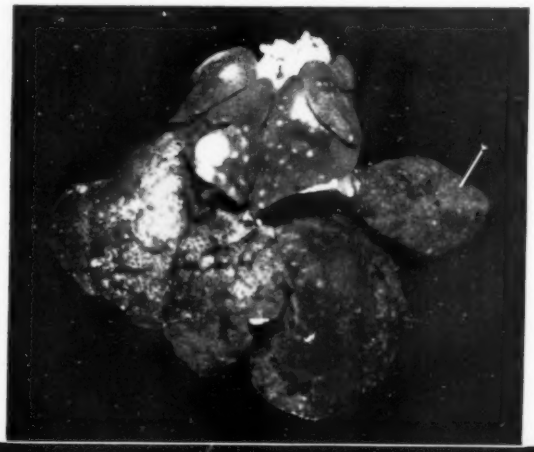

FIG. 2

FIG. 1. Organs of seventy-six day old offspring from mother guinea pig given intravenous injection of 0.01 mg. virulent human tubercle bacilli nine days prior to birth of young. Note generalized organ tuberculosis. This is not the usual finding after nine days *in utero*.

FIG. 2. Absence of specific tuberculo-immunity in offspring of mothers heavily infected intravenously.

Left. Control given a subcutaneous injection of 0.000,1 mg. of virulent human tubercle bacilli (H160) and examined sixty-one days after infection. Note generalized tuberculosis.

Right. Offspring born ten days after the mother had received 0.01 mg. of virulent human tubercle bacilli (H160) intravenously. This young was infected subcutaneously when eighty days old, the same as above control. Sixty-one days after infection, the organs of the offspring showed about the same amount of general tuberculosis as the control indicating the absence of any notable specific immunity.

at least in the usual case and possibly as long as twelve days in the average case. Such passage fails to take place in spite of the fact that the mother guinea pig succumbs to this intravenous infection with virulent human tubercle bacilli within one to two weeks after birth of the offspring and the additional fact that

as little as 0.000,001 mg. or less will serve to produce generalized tuberculosis in a guinea pig injected subcutaneously or intravenously with this amount of virulent bacilli. One exception occurred in one offspring guinea pig which was born nine days after the infection of the mother. This young pig was tuberculin positive when tested one month after birth and was killed seventy-six days after birth. It revealed a generalized tuberculosis (see figure 1). This is not the usual finding but indicates that it can occur under certain circumstances.

PRESENCE OF TUBERCULO-ALLERGY AND SPECIFIC TUBERCULO-IMMUNITY IN OFFSPRING FROM MOTHER GUINEA PIGS HEAVILY INFECTED INTRAVENOUSLY WITH VIRULENT HUMAN TUBERCLE BACILLI

In order to note whether heavily intravenously infected pregnant guinea pigs transmitted tuberculo-allergic hypersensitiveness or the essentials for specific tuberculo-immunity to their offspring, a series of such guinea pigs was given an intravenous injection (ear vein). The viable offspring born to them were

TABLE 3

Transmission of tuberculo-allergic hypersensitiveness and specific tuberculo-immunity from heavily infected pregnant guinea pigs to their offspring

DAYS IN UTERO AFTER INTRAVENOUS INFECTION OF MOTHER WITH 0.01 MG. VIRULENT HUMAN TUBERCULE BACILLI (H160)	DAYS AFTER INFECTION WHEN MOTHER DIED	TUBERCULIN TEST 1:100 SEITZ FILTRATE INTRACUTANEOUSLY		TUBERCULOSIS IN OFFSPRING 61 DAYS AFTER THE SUBCUTANEOUS INFECTION WITH 0.000,1 MG. H 160, 3 TO 21 DAYS AFTER TUBERCULIN TEST
		Age of offspring in days	Tuberculin reaction	
1	22	54	0 0	3* 4
4	40	51	0 0 0	2 3 2
8	14	47	0 0	2 2
8	17	32	0 0	3 2
9	15	31	0 0	2 3
10	27	77	0 0	4 3
Infection controls, 5 guinea pigs			0 0 0 0 0	3 2 3 2 2

* The amount of tuberculous involvement is graded arbitrarily from 0 = no visible macroscopical organ involvement, to 4 = a general massive involvement of all the important internal organs and lymph nodes.

studied both for tuberculo-allergic hypersensitiveness (tuberculin skin reaction) and specific tuberculo-immunity against virulent infection. The results of these studies are recorded in table 3.

It is evident from the findings recorded in table 3 that virulent human tubercle bacilli given intravenously to pregnant guinea pigs are not transferred to the offspring *in utero*, as determined by infection of the offspring, as well as culture shown in the previous experiment, in spite of the fact that the intravenous infection with highly virulent bacilli is so overwhelming that the mother guinea pigs survive only a few weeks. As would be expected from this and previous studies, neither tuberculo-allergy nor tuberculo-immunity are transferred to the offspring (figure 2), although one must admit that ten days is not the period of maximum development of specific tuberculo-immunity nor of tuberculo-allergic hypersensitiveness. The overwhelming infection may have prevented such normal development of allergic hypersensitiveness or specific immunity even in the mother. However, since the offspring developed normally after birth and since the allergic and specific immune antigen was overwhelmingly present in the mother, it appears that it might be assumed that the antigenic or such materials as actively stimulate the formation of specific tuberculo-immune bodies or tuberculo-allergic hypersensitiveness also were not transferred from mother to offspring within this period. This appears to parallel similar findings previously obtained, indicating that tuberculo-allergic hypersensitiveness and specific tuberculo-immunity must be produced actively in the host and cannot be transferred passively or passed from mother to offspring. The findings recorded in table 3 present no evidence that the young born to these overwhelmingly infected mothers possessed any more specific immunity than the controls born to normal mothers.

SUMMARY AND CONCLUSIONS

1. A relatively large intravenous (0.01 mg.) injection of highly virulent human tubercle bacilli into a pregnant guinea pig does not result in the passage of the bacilli to the offspring (foetus) for at least up to nine days in the usual case and possibly for as long as twelve days in the average case. Such passage does not occur in spite of the fact that the mother guinea pig succumbs to this intravenous virulent infection within one to two weeks after birth of the offspring.

2. The offspring from heavily intravenously infected mother guinea pigs do not develop any discernible specific tuberculo-immunity, as determined by infection tests, nor specific tuberculo-allergic hypersensitiveness, as tested by the skin tuberculin reaction.

3. In spite of the fact that viable avirulent human tubercle bacilli given intravenously in amounts as high as 1 mg. produce an excellent specific tuberculo-immunity and a definite specific tuberculo-allergic hypersensitveness to tuberculin in the mother guinea pig and that there is plenty of time *in utero* for the passage of this specific tuberculo-immunity and specific allergic-hypersensitiveness, no evidence of such passage to the offspring was noted.

SUMARIO Y CONCLUSIONES

1. Una inyección intravenosa relativamente grande (0.01 mg.) de bacilos tuberculosos humanos muy virulentos en una cobaya embarazada no hizo pasar los bacilos a la prole (feto) por lo menos en un plazo de nueve días habitualmente y posiblemente hasta de 12 días en la mayoría de los casos. Ese pase no tiene lugar aunque la cobaya sucumba a esa infección virulenta endovenosa en un término de una a dos semanas después de dar a luz.

2. La prole de las cobayas infectadas intensamente por vía venosa no manifiesta la menor tuberculoinmunidad específica descubrible en lo que puedan determinar las pruebas de infección ni hipersensibilidad tuberculosa alérgica específica en lo que determina la cutirreacción de la tuberculina.

3. A pesar de que los bacilos tuberculosos humanos avirulentos viables inyectados intravenosamente a dosis hasta de 1 mg. producen una excelente tuberculoinmunidad específica y una hipersensibilidad tuberculoalérgica bien definida a la tuberculina en la cobaya embarazada y que hay suficiente tiempo *in utero* para el pase de la tuberculoinmunidad y la alergohipersensibilidad específicas, no se ha observado ningún signo de tal transmisión a la prole.

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THE ACTION OF SOME DERIVATIVES OF 4-4′DIAMINODIPHENYLSULFONE IN EXPERIMENTAL TUBERCULOSIS[1]

M. I. SMITH, E. W. EMMART AND E. F. STOHLMAN

Previous work has shown (1) that, in a series of sulfonamides, sulfones and certain related phosphorus compounds, 4-4′diaminodiphenylsulfone was the most effective agent in inhibiting the growth of the tubercle bacillus *in vitro*. In guinea pigs it was possible to retard the tuberculous process by the daily oral administration of this compound in doses of about 75 per cent of the minimum fatal dose given over a period of thirty days. The excessive toxicity of this compound appeared to warrant a systematic search for less toxic and possibly more effective derivatives. Accordingly the following compounds were examined in an attempt to evaluate their effectiveness in experimental tuberculosis in relation to their toxicity as compared with the parent sulfone or its sulfonated glucose derivative (promin), both of which have been studied in considerable detail previously (1):

1: 4-nitro 4′aminodiphenylsulfone[2]
2: Sodium 4-4′diaminodiphenylsulfone bis-formaldehyde sulfoxylate (2)
3: 4-amino 4′hydroxydiphenylsulfone[2]
4: N-phosphoryl derivative of diaminodiphenylsulfone (3)

The technique employed was very similar to that previously described (1). The acute and chronic toxicity of the compounds was studied in guinea pigs. The blood concentration of the drugs in relation to dosage was ascertained by the method of Bratton and Marshall (4). The tuberculostatic action of the compounds *in vitro* was ascertained by determining the minimal effective concentration required to inhibit the growth of the tubercle bacillus (human strain A27, Henry Phipps Institute) on glycerine bouillon. Lastly, the therapeutic effectiveness of the compounds was evaluated in guinea pigs inoculated intraperitoneally with the human strain A27 grown on glycerine bouillon or H37RV (Trudeau Laboratories) grown on Proskauer and Beck medium.

TOXICITY, DOSAGE, HAEMATOLOGY AND BLOOD LEVELS IN GUINEA PIGS

The compound 4-nitro 4′aminodiphenylsulfone is insoluble in water, its absorption when given orally in aqueous suspension is irregular and its toxicity is quite variable. Single doses of 0.5 g. per kg. usually produced hyperexcitability and often proved fatal. Repeated doses of 0.2 g. per kg. given daily appeared to be the maximum that could be tolerated with safety. The latter was the dose chosen in the therapeutic tests.

The formaldehyde sulfoxylate and the N-phosphoryl derivatives were well tolerated in daily doses of 0.5 and 1.0 g. per kg. as shown by the weight curves

[1] From the Division of Chemotherapy, National Institute of Health, U. S. Public Health Service, Bethesda, Maryland.

[2] Kindly supplied by Dr. G. W. Raiziss, Dermatological Research Laboratories.

in chart 1. As pointed out previously (3), guinea pigs tolerate single doses of 1.5 g. per kg. of the N-phosphoryl derivative with only minor toxic manifestations. Promin by contrast is tolerated well in doses of only 0.5 g. per kg., while 1.0 g. per kg. doses are distinctly toxic. The 4-amino 4′hydroxydiphenylsulfone is well tolerated in doses of 1.0 g. per kg. For comparative purposes, however,

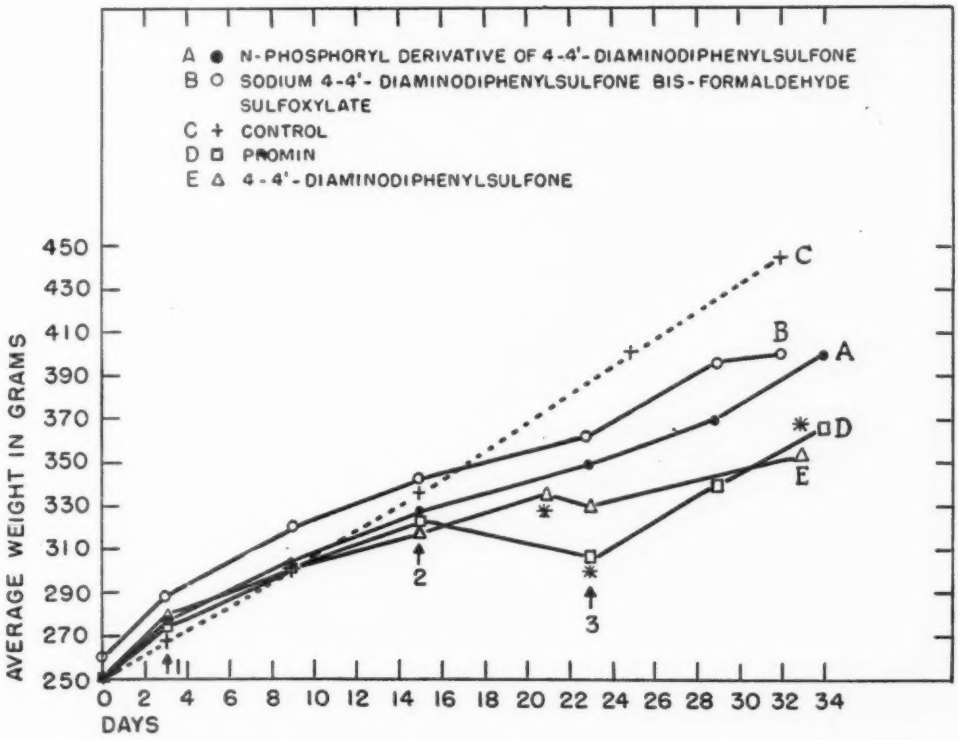

CHART 1. The effects of daily doses of three derivatives of 4-4′diaminodiphenylsulfone in comparison with the parent substance on the weight curve and survival of normal guinea pigs. At first arrow 0.15 g. per kg. of the sulfone and 0.5 g. per kg. of all the other compounds were administered orally daily; at the second arrow 0.3 g. per kg. of the sulfone and 1.0 g. per kg. of the derivatives were given; and at third arrow 0.2 g. per kg. of the sulfone and 0.5 g. per kg. of the derivatives were given to the end of the experiment. There were 8 animals to each group. Asterisk indicates death of an animal. It will be seen that 4-4′diaminodiphenylsulfone and promin were the most toxic, and the N-phosphoryl and sulfoxylate derivatives the least toxic.

these four drugs were given in doses of 0.5 g. per kg. daily in the therapeutic tests. The parent substance 4-4′diaminodiphenylsulfone was given daily in doses of 0.15 to 0.2 g. per kg., which is the limit of safety for this compound.

The effects of some of the foregoing compounds in the dosages indicated are shown on the weight curves of young growing guinea pigs in chart 1.

Haemoglobin determinations and red and white cell counts were made of the

guinea pigs charted in chart 1 during and at the end of the experimental period. The results of these experiments, shown in table 1, indicate that the parent sulfone is the most toxic to the haematopoietic system and the formaldehyde sulfoxylate derivative the least toxic. Blood smears showed a variable degree of polychromatophilia, anisocytosis, Howell-Jolly bodies, normoblasts, immature myelocytes and degenerating leucocytes ("basket cells"). These changes were most marked in the parent sulfone and promin groups. Spectrophotometric examination of the blood from time to time indicated methemoglobin formation in the groups receiving the parent sulfone and promin, not in the others.

TABLE 1

Haematologic studies

COMPOUND	HAEMOGLOBIN, GM./100 CC.			RED CELLS MILL./CU.MM.		WHITE CELLS PER CU. MM.	
	Minimum	Maximum	Average	At twenty-one days	At thirty days	At twenty-one days	At thirty days
Controls	13.7	15.0	14.2	4.8	5.3	5,000	6,500
4-4′diaminodiphenylsulfone	10.3	12.7	11.5	4.1	3.6	13,400	16,300
Promin	10.0	12.5	11.5	2.9	4.3	15,000	8,500
N-phosphoryl derivative of 4-4′diaminodiphenylsulfone	9.6	12.5	11.2	3.5	3.1	12,500	8,900
Sodium 4-4′diaminodiphenylsulfone bis-formaldehyde sulfoxylate	10.5	14.2	11.9	3.6	4.1	10,000	9,800

TABLE 2

Blood levels at the end of thirty days of treatment

COMPOUND AND DAILY DOSAGE	BLOOD CONCENTRATION MG PER CENT			
	2 hours	4 hours	6 hours	24 hours
4-4′diaminodiphenylsulfone, 0.15 to 0.2 g. per kg.	6.4	6.4	5.2	0.5
Promin, 0.5 g. per kg	2.7	4.0	3.6	trace
N-phosphoryl derivative of 4-4′diaminodiphenylsulfone 0.5 g. per kg	8.4	7.7	7.0	2.0
Sodium 4-4′diaminodiphenylsulfone bis-formaldehyde sulfoxylate, 0.5 g. per kg	1.8	3.1	2.4	0.7
4-amino 4′hydroxydiphenylsulfone 0.5 g. per kg.	5.3	2.7	1.9	trace

The differences in the red and white cell counts at the twenty-one and thirty day periods, as seen in table 1, appear to be related to change in dosage, as shown in chart 1, and seem to indicate that the effects of the parent sulfone are progressive and cumulative while those of some of the derivatives are more transitory in character.

The results of blood level determinations at the end of the experimental period of the animals charted in chart 1 are given in table 2. The figures represent

averages of two to four experiments giving the values obtained after hydrolysis with hydrochloric acid. The sulfone and the derivatives studied are apparently not conjugated in the guinea pig and the values for "free" and "total" drug are very nearly the same in most cases. The data appear to indicate that the parent sulfone and its phosphoryl derivatives are best retained, promin and the hydroxy compound are less well retained, while the sulfoxylate compound is poorly absorbed and little retained in the guinea pig. Higher blood levels were obtained with subcutaneous injections of the sulfoxylate derivative, but retention was no better. Thus in a series of guinea pigs receiving 10 to 13 daily doses of 0.5 g. per kg. subcutaneously, the average blood level was 12.8 mg. per cent one hour after the last injection, 7.0 mg. per cent at three hours and 0.8 mg. per cent at six hours. None was found in the blood twenty-four hours after the last injection.

THE TUBERCULOSTATIC ACTION

The extreme insolubility of the nitro derivative made it impossible to determine its inhibiting action *in vitro*. The inhibiting action of the other compounds against the human strain A27 was relatively high compared with that of promin, which was previously reported (1), and usually not as high as that of the parent sulfone. The concentrations of the several compounds required to produce partial to complete inhibition of growth were as follows:

4-4′diaminodiphenylsulfone	1 to 7 mg. per cent
N-Phosphoryl derivative of 4-4′diaminodiphenylsulfone	4 to 10 mg. per cent
4-amino 4′hydroxydiphenylsulfone	5 to 10 mg. per cent
Sodium 4-4′diaminodiphenylsulfone bis-formaldehyde sulfoxylate	5 to 10 mg. per cent
Promin	20 to 100 mg. per cent

From this it would appear that the bacteriostatic action of the phosphoryl compound, though somewhat less than that of the parent sulfone, is considerably greater than that of promin.

THERAPEUTIC TESTS IN GUINEA PIGS

These were carried out in two series of experiments. In the first the A27 strain was used, with an infective dose of 0.5 mg. tubercle bacilli, moist weight, given intraperitoneally. Fifteen animals were used in each of the control and treated groups. In this series the drugs used were the parent sulfone, the nitro derivative and the sodium formaldehyde sulfoxylate derivative. In the second series the human strain H37RV was used in the same dosage as above and 20 animals were employed in each of the control and treated groups. The drugs used in this series were promin, 4-amino 4′hydroxydiphenylsulfone and the N-phosphoryl derivative of the sulfone. Promin served as a standard of reference in the second series of experiments and the parent sulfone in the first. Treatment was begun the day following inoculation and continued for one month.

Dosages used were as indicated previously. All soluble drugs except the sulfoxylate were administered in solution by stomach tube while the insoluble sulfone and the nitro derivative were given in like manner in aqueous suspension. The sulfoxylate was given subcutaneously because of its poor absorbability from the gastrointestinal tract. The first experiment was terminated fifty-seven days and the second ninety-five days after inoculation. At necropsy the amount of tuberculous involvement was noted in the omentum and lymph nodes, the spleen,

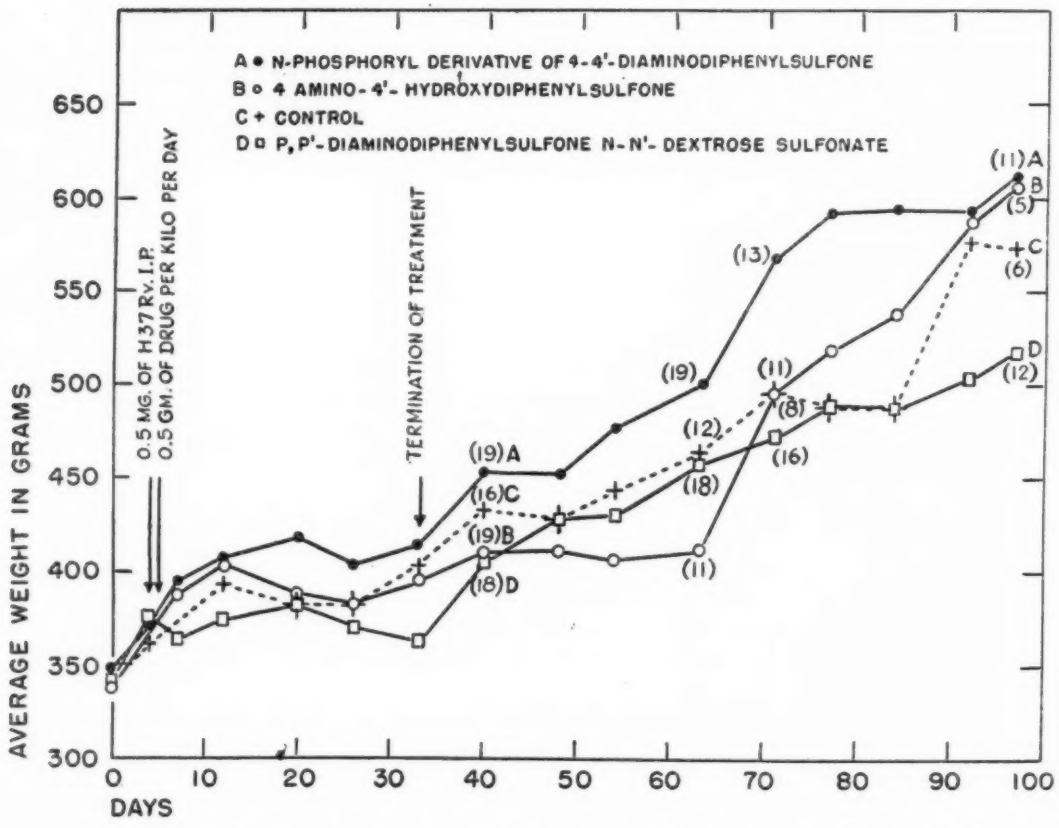

CHART 2. The average weight curve and survival rate of three groups of tubercle infected guinea pigs treated for thirty days with three derivatives of 4-4'diaminodiphenylsulfone. There were 20 guinea pigs to each group. Figures in parentheses indicate the number of survivors in each group.

the liver, the lungs and the peritoneum and kidneys; and each was rated on the basis of 0 to 4 according to the extent of involvement. The sum of these gives the "tuberculosis index" for each animal, and the sum of these divided by the number of animals gives the "average tuberculosis index" for the group.

The degree of tuberculous involvement in the first series of experiments and the percentage mortality at the time of its termination, fifty-seven days after inoculation, were as follows:

	AVERAGE TUBERCULOSIS INDEX	PER CENT MORTALITY
Controls	6.6	67
4-4′diaminodiphenylsulfone	3.6	7
4-nitro 4′aminodiphenylsulfone	3.6	27
Sodium 4-4′diaminodiphenylsulfone bis-formaldehyde sulfoxylate	5.4	67

Analysis as to the amount of tuberculous involvement in the several viscera in the four groups showed the following:

	OMENTUM AND LYMPH NODES	SPLEEN	LIVER	PERITONEUM AND KIDNEYS	LUNGS
Controls	2.1	1.0	1.4	0.5	1.5
4-4′diaminodiphenylsulfone	2.0	0.5	0.2	0.2	0.7
4-nitro 4′aminodiphenylsulfone	1.7	1.1	0.3	0.1	0.4
Sodium 4-4′diaminodiphenylsulfone bis-formaldehyde sulfoxylate	2.1	1.4	1.5	0.1	0.3

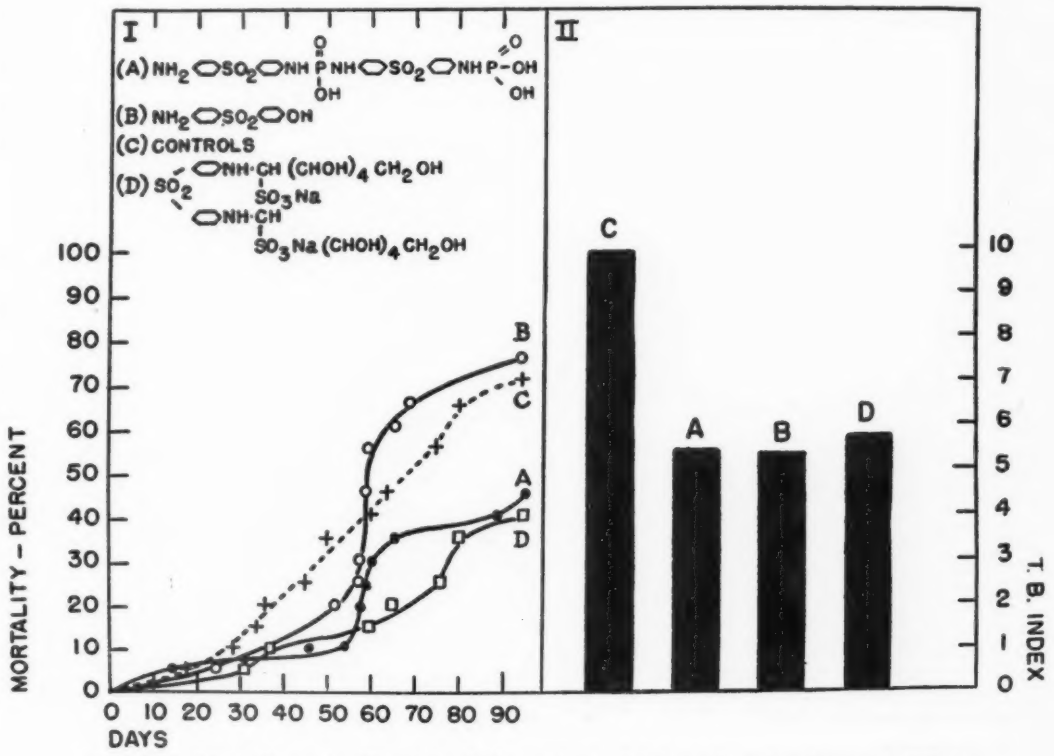

CHART 3. Mortality rate (I), and relative extent of tuberculous involvement (II) in three groups of guinea pigs treated with three derivatives of 4-4′diaminodiphenylsulfone for thirty days in comparison with nontreated controls. Twenty guinea pigs to each group.

The conclusion that may be drawn from this series of experiments is that the parent sulfone was the most effective drug, the nitro derivative somewhat less effective and the formaldhyde sulfoxylate derivative scarcely, if at all, effective.[3] It would also appear that none of the drugs completely prevented tubercle formation in any of the organs, though the more effective the drug the less tendency for the dissemination of the tuberculous process from the site of inoculation to distant organs. This may be explained on the basis of some recent experiments indicating that the beneficial effects of this type of drug are possibly due to an attenuating action on the bacillus (6).

The results of the second series of experiments are summarized in charts 2 and 3. Chart 2 shows the average weight curves of the controls and treated animals until the termination of the experiment at ninety-five days after inoculation. The figures in parentheses on each curve indicate the number of animals surviving at the particular period of the experiment. The weight curve of the animals treated with the N-phosphoryl derivative was distinctly better than that of the controls or any of the other treated groups, including promin. In chart 3 the mortality rate and the "average tuberculosis index" for the several groups are shown. Seventy per cent of the controls and 75 per cent of the group treated with the hydroxy derivative were dead at the time the experiment was terminated as against 40 per cent for the promin group and 45 per cent for the group treated with the N-phosphoryl derivative. The extent of tuberculous involvement of the viscera in the several groups was as follows:

	OMENTUM AND LYMPH NODES	SPLEEN	LIVER	PERITONEUM AND KIDNEYS	LUNGS	TOTAL
Controls	2.3	1.8	1.9	1.4	2.4	9.8
Promin	0.9	0.7	1.1	0.8	2.2	5.7
N-phosphoryl derivative of the sulfone	1.0	0.7	0.9	0.8	2.1	5.5
4-amino 4'hydroxydiphenylsulfone	1.0	0.6	0.7	0.6	2.5	5.4

Considering the degree of tuberculous involvement, the weight curves and the percentage survival, it appears that the N-phosphoryl derivative has an advantage over promin. Promin is about one-third the molar equivalent of the parent sulfone and is nearly equal in therapeutic activity to the sulfone when given in weight for weight dosage of about three times that of the sulfone (1). The N-phosphoryl derivative is considerably better than the parent sulfone, since nearly equivalent effects have been obtained from less than one-third of its tolerated dose as compared with about 75 per cent of the tolerated dose of the parent sulfone. By our criteria, however, none of the drugs so far tested

[3] At this writing, a paper has appeared by F. T. Callomon (5) reporting favorable results with the formaldehyde sulfoxylate derivative of diaminodiphenylsulfone in experimental guinea pig tuberculosis. The drug was administered orally in doses of 0.6 to 1.0 g. per kg. daily for four weeks, and the experiment was terminated six weeks after infection.

is sufficiently effective in completely preventing experimental tuberculosis in guinea pigs, though some of them appear to be capable of ameliorating the disease to a considerable extent.

SUMMARY

A study has been made of the toxicity, blood levels, tuberculostatic action, and therapeutic effectiveness in experimental guinea pig tuberculosis of five derivatives of 4-4′diaminodiphenylsulfone in comparison with the parent substance. Consideration of all the factors involved indicates that the N-phosphoryl derivative of diaminodiphenylsulfone is superior to the sulfonated glucose derivative (promin) which in turn is better than the nitro, hydroxy, or the sodium formaldehyde sulfoxylate derivatives.

SUMARIO

Estúdianse en este trabajo la toxicidad, tensión sanguínea, acción tuberculostática y eficacia terapéutica en la tuberculosis experimental del cobayo, de cinco derivados de la diaminodifenilsulfona 4-4′, comparándolos con la substancia matriz. Una consideración de todos los factores comprendidos indica que el derivado N-fosforílico de la diaminodifenilsulfona resulta superior al derivado de la glucosa sulfonada (promina), que a su vez es mejor que los derivados nitro, hidroxi, o sódico del sulfoxilato formaldehídico.

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EFFECT OF AROMATIC IODINE COMPOUNDS ON THE TUBERCLE BACILLUS[1,2]

ARTHUR K. SAZ, FRANK R. JOHNSTON, ALFRED BURGER AND FREDERICK BERNHEIM

When benzoic or o-hydroxybenzoic acid is added to a washed suspension of virulent tubercle bacilli of the B_1 or H37 strains a marked increase in oxygen uptake occurs (1). This is probably due, in part at least, to the oxidation of these compounds by the bacteria, for it has been shown that a nonpathogenic species of mycobacteria definitely oxidizes benzoic acid (2). This latter species also oxidizes p- and m-hydroxybenzoic acids but not the ortho isomer and is able to utilize either of the first two compounds or benzoic acid as the sole source of carbon for growth (3). On the other hand the addition of benzoic or o-hydroxybenzoic acid to veal infusion broth or Long's synthetic medium does not affect the growth of the tubercle bacillus, except in comparatively large concentrations when inhibition occurs (3). We assumed, however, that the oxidation of benzoic and o-hydroxybenzoic acid represents an important metabolic reaction of the tubercle bacillus and have therefore tested the effect of a number of substituted benzoic and sulfonic acids and phenols on the growth of these bacteria *in vitro* and *in vivo*, as well as their effect on the oxygen uptake of the bacterial suspensions. In a previous report (4), we showed that 2,3,5-triiodobenzoic and 3,5-diiodo-2-hydroxybenzoic acids are effective inhibitors of growth *in vitro*, whereas a number of other compounds are ineffective. These results supported the assumption that these drugs were inhibiting growth by interfering with the utilization of benzoic acid and related compounds by the tubercle bacillus and emphasized that iodine substitution in the ring greatly enhanced the inhibitory action. We have, therefore, tested a number of iodine substituted aromatic compounds for (*a*) their effect on the oxygen uptake of washed suspensions of tubercle bacilli; (*b*) their effect on growth *in vitro*; (*c*) their toxicity and distribution in the body; (*d*) their effect on the growth of the tubercle bacillus in the guinea pig.

EXPERIMENTAL

Table 1 gives the formulae of the compounds used; 2,3,5-triiodobenzoic acid, 3,5-diiodo-2-hydroxybenzoic acid, and 3,5-diiodo-4-hydroxybenzoic acid were obtained from the Eastman Kodak Co. and recrystallized before use. The sozoiodolate (3,5-diiodo-4-hydroxybenzene sulfonic acid) was obtained as the sodium salt from Eimer and Amend. The 2,4,6-triiodophenol and its ethers were synthesized by one of us (A.B.) according to the procedure of Long and

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[2] This paper covers in part the dissertation submitted by Arthur K. Saz in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Graduate School of Duke University.

Burger (5). The synthesis of 2,4,6-triiodobenzoic acid is described below. The triiodobenzene sulfonic acids were synthesized according to the method of Boyle (6). The compounds did not exhibit the physical properties described by Boyle (6). They crystallized from water as shining leaflets without water of crystallization. They did not melt below 350°C. but decomposed at high temperatures. For analysis the samples were dried at 130°C. and 2 mm. over phosphorus pentoxide.

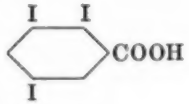
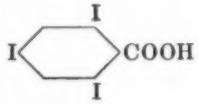
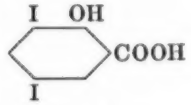
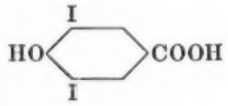
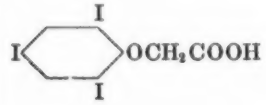
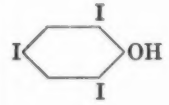
Analysis: Calculated for $C_6H_3I_3O_3S$: C, 13.44; H, 0.67.
Found for 2,3,5-triiodobenzene sulfonic acid: C, 12.54, 12.00; H, 1.38, 1.09.
Found for 2,4,5-triiodobenzene sulfonic acid: C, 13.36; H, 0.77.

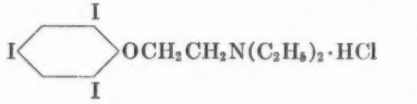
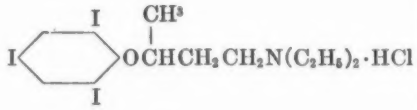
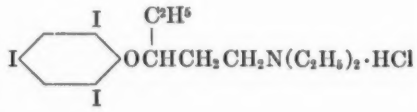
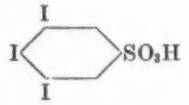
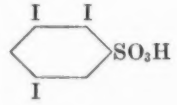
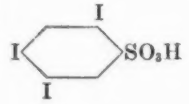
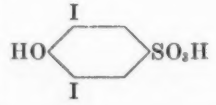
The synthesis of 2,4,6-triiodobenzoic acid was carried out as follows. One and one-half grams of 2,4,6-triiodotoluene was heated in a sealed tube with 6 cc. of 15 per cent nitric acid at 180° to 190°C. for six hours. The dark solid was filtered, washed with water and treated with hot dilute sodium hydroxide solution. The mixture was cooled, filtered and the filtrate washed with ether. The alkaline solution was acidified, and the red voluminous precipitate filtered and washed with water. It was then suspended in 5 cc. of concentrated hydrochloric acid containing 0.5 g. of stannous chloride, and the mixture allowed to stand for two hours with occasional gentle warming. The solid was filtered, washed with water and recrystallized from dilute ethanol with the aid of darco. The almost colorless crystals sintered at 217°C. and melted at 230° to 235°C. with decomposition. The yield was 0.1 g.

The compounds can be divided into three groups: iodobenzoic acids, triiodophenol and its ethers, and triiodobenzene sulfonic acids. Their effects on the oxygen uptake and growth *in vitro* of the tubercle bacillus and their toxicity to guinea pigs are summarized in table 1. The H37 and B_1 strains used react identically to all the compounds.

(*a*) *Oxygen uptake:* The bacteria were grown on veal-glycerine infusion broth and a suspension was washed and prepared by the method already described (1). The measurements were made in Warburg vessels in each of which approximately 50 mg. of bacteria were suspended in 2.0 cc. of 0.05 M phosphate buffer, pH 6.7. The control respiration signifies the oxygen uptake of the suspensions without any addition of substrate. The benzoate and salicylate effects refer to the extra oxygen uptake which occurs when 1.0 mg. of one or the other compound is added to the suspension. The compounds were added as sodium salts dissolved in buffer at pH 6.7. All the drugs were neutralized before they were added. In the iodobenzoic acid group the two triiodobenzoic acids behave in exactly the same way. In a concentration of 50 mg. per cent they inhibit the control oxygen uptakes approximately 30 per cent and the benzoate and salicylate effects approximately 80 per cent and 75 per cent, respectively. As the concentration is lowered the inhibition of the control oxygen uptake disappears, first followed by the inhibition of the salicylate effect. The benzoate effect is most sensitive to these drugs. The triiodobenzoates do not, in any concentration range, increase the control oxygen uptakes. The 3,5-diiodo-2-hydroxybenzoic

TABLE 1

COMPOUND	FORMULA	EFFECT ON OXYGEN UPTAKE				EFFECT ON GROWTH			TOXICITY OF 60 MG./KG. PER OS DAILY TO GUINEA PIGS
		Concentration	Control uptake	Benzoate effect	Salicylate effect	Concentration	Effect	Action	
		mg. %				*mg. %*			
2,3,5-triiodobenzoic acid		50 10	30% I no I	85% I 82% I	74% I 53% I	5.0	100% I	BS	Tolerated thirty days at least without weight loss
2,4,6-triiodobenzoic acid		50	36% I	82% I	75% I	5.0	83% I	—	
3,5-diiodo-2-hydroxy-benzoic acid		50 20	no I 150% A	85% I —	85% I —	5.0	100% I	BC	Death in four to six days
3,5-diiodo-4-hydroxy-benzoic acid		20	no I	no I	25% I	10.0	40% I	—	
2,4,6-triiodophenoxy-sodium acetate (B14)		15	36% I	85% I	no I	3.0	45% I	—	Death in two to three days
2,4,6-triiodophenol (B29)		15	100% A	—	—	3.0	67% I	BS	Tolerated fourteen days at least with 0–10 gm. weight loss

1-diethylamino 2-(2,4,6-triiodophenoxy)ethane HCl (B9)		50	100% A	—	—	3.0	100% I	BS	Tolerated fourteen days at least with 20–80 gm. weight loss
1-diethylamino-3-methyl-3-(2,4,6-triiodophenoxy)propane HCl (B7)		25	93% A	—	—	3.0	100% I	BC	Death in five to seven days
3-(2,4,6-triiodophenoxy)-1-diethylaminopentane HCl (B30)		50	65% A	—	—	3.0	100% I	BC	Death in four to six days
3,4,5-triiodobenzene sulfonic acid		50	no I	no I	no I	10.0	no I	—	
2,3,5-triiodobenzene sulfonic acid		50	no I	42% I	78% I	10.0	no I	—	
2,4,5-triiodobenzene sulfonic acid		50	no I	66% I	52% I	10.0	no I	—	
sozoiodolic acid		50	no I	no I	81% I	10.0	no I	—	

I signifies inhibition. A signifies acceleration. BS signifies bacteriostatic. BC signifies bactericidal.

acid in a concentration of 50 mg. per cent has no effect on the control oxygen uptake but inhibits the benzoate and salicylate effects. In lower concentrations it markedly increases the control uptake and this obscures any effect it may have on the action of benzoate and salicylate. On the other hand, 3,5-diiodo-4-hydroxybenzoic acid has no effect on the control uptake at any concentration and little or no effect on the action of benzoate and salicylate.

Small amounts of triiodophenol and its basic ethers markedly increase the control oxygen uptake but higher concentrations have no effect or even inhibit. This increase obscures any effect they may have on the action of benzoate and salicylate. It is interesting that this increase in the control uptake caused by triiodophenol and its basic ethers can be inhibited by the triiodobenzoic acids or B14. Thus these two types of compounds acting in different ways on the respiration of the tubercle bacillus can counteract each others effects.

None of the triiodobenzene sulfonic acids have any marked effect on the control oxygen uptake in a concentration of 50 mg. per cent, and do not increase it at lower concentrations. The effect on the action of benzoate and salicylate is different for each compound.

(*b*) *Growth in vitro:* All the experiments were done on veal-glycerine infusion broth. The drugs after neutralization were added to the media before autoclaving. Inorganic iodine was not split off any of the compounds, and potassium iodide in a concentration of 15 mg. per cent had no effect on the growth. At the end of the experiment the cultures were autoclaved, filtered and the dry weight of the bacteria obtained. The figures represent the average of five bottles. In order to determine whether a drug was bacteriostatic or bactericidal, a culture, the growth of which had been completely inhibited by the drug for ten days, was removed and placed in fresh control media. If growth then occurred the drug was bacteriostatic, but if no growth occurred it was assumed to be bactericidal. Table 1 shows that there is no correlation between the effect of a compound on the oxygen uptake and its effect on growth. There is a remarkable difference between the triiodobenzoic acids and the triiodobenzene sulfonic acids. The latter group has no effect on the growth whereas the former are very effective inhibitors. Even in concentrations of 1.0 mg. per cent the triiodobenzoic acids cause an inhibition of more than 50 per cent. If the drugs are added during the logarithmic growth phase instead of at the time of inoculation, inhibition also occurs but about twice the concentration is necessary to produce equivalent effects under these conditions.

(*c*) *Toxicity:* Preliminary toxicity experiments were done on guinea pigs with all the drugs that were effective inhibitors of growth *in vitro* with the exception of 2,4,6-triiodobenzoic acid, which we had in amounts insufficient to carry out such tests.

Table 1 shows that all the bactericidal compounds were too toxic for testing their possible effects on the tubercle bacillus *in vivo*. In the iodobenzoic acid group the difference between 2,3,5-triiodobenzoic acid and 3,5-diiodo-2-hydroxybenzoic acid is very marked. The former can be fed daily to guinea pigs for a period of six weeks in dosages of 70 to 80 mg./kg. without any signs of

toxicity. In man also 50 mg./kg. can be taken daily for six weeks without toxic symptoms, even though the blood concentration may rise to 40 mg. per cent. On the other hand, the latter compound causes death in guinea pigs in four to six days when fed in doses of 60 mg./kg. In the triiodophenol group the free phenol is the least toxic. As the length of the side chain increases ethers become more toxic and B7 and B30 cause death after feeding 60 mg./kg. for four days. B14 which is not a very effective inhibitor of growth *in vitro* is also toxic. The toxicity of the triiodobenzenesulfonic acids was not tested because they were ineffective growth inhibitors. These preliminary results leave 2,3,5-triiodobenzoic acid, B9 and B29 as possible chemotherapeutic agents to be tested for their effect on the growth of the tubercle bacillus in the guinea pig.

(*d*) *Distribution and excretion of 2,3,5-triiodobenzoic acid, B9 and B29:* In order to follow the distribution and excretion of the drug the iodine method of Kendall (7) was used. There was no evidence of the presence of inorganic iodine in the

TABLE 2

The determination of various compounds in normal and tuberculous tissues

The rabbits were fed 60 mg./kg. daily for a week. The children were fed 30 mg./kg. for four days

TISSUE	NORMAL RABBIT FED 2,3,5-TRI-IODO-BENZOIC ACID	NORMAL RABBIT FED B29	NORMAL RABBIT FED B9	TUBERCULOUS RABBIT FED B9	CHILD WITH TUBERCULOUS MENINGITIS FED 2,3,5-TRIIODO-BENZOIC ACID	CHILD WITH TUBERCULOUS MENINGITIS FED B9
	mg.%	*mg.%*	*mg.%*	*mg.%*	*mg.%*	*mg.%*
Liver.....	7.8	trace	12.8	31.6	29.0	42.0
Lung.....	12.7	2.1	trace	29.4	43.0	63.0
Kidney.....	trace	22.0	15.4	65.0	—	24.0
Spleen.....	trace	43.0	6.0	19.2	29.0	48.0
Muscle.....	trace	9.4	26.8	6.1	—	—
Heart.....	11.0	trace	6.6	19.5	—	—
Brain.....	19.2	7.3	42.5	1.9	—	—
Bone.....	—	15.4	—	3.8	21.0	—
Blood.....	12.1	7.1	18.0	27.0	41.0	12.0

urine after administration of any drug, indicating that iodine is not split off the ring in the body. Whether the drugs are conjugated or otherwise altered in the body has not been determined. The drugs were fed daily to rabbits in a dosage of 60 mg./kg. by stomach tube for five to seven days. The urine and faeces were collected and at the end of the experiment the rabbit was killed and the tissues analyzed. Table 2 gives the results in mg. per cent. The urinary excretion of B9 and 2,3,5-triiodobenzoic acid average 15.0 mg. daily and only small amounts were found in the faeces. For B29 the excretion averaged 190 mg. daily. This indicates that the first two drugs tend to accumulate and suggests that after feeding them for a few days at the higher levels it might be possible to reduce the dosage considerably.[3] The recovery of 2,3,5-triiodobenzoic averaged only 20

[3] The effects of accumulation can be seen particularly in the case of B9. Normal guinea pigs were fed daily for twelve days with doses varying from 15 to 75 mg./kg. All showed

to 30 per cent of the amount given, indicating that it may be stored in tissues such as the skin, fat and thyroid which were not analyzed. The recovery of B9 averaged 60 per cent and of B29, 90 per cent. One rabbit was inoculated with 0.4 mg. of the B_1 strain intraperitoneally and the disease allowed to progress for two weeks before B9 was fed daily for one week. The tissue analyses at the end of this time showed that the liver, kidney and spleen contained considerably more of the drug than these organs contained in the normal rabbit and that these increases were at the expense of the brain and muscle. This indicates that the drug accumulates in the organs where the tuberculosis is actively progressing. One child in coma with tuberculous meningitis accompanied by a miliary spread in the lungs was given 30 mg./kg. of B9 by mouth for four days and the tissues analyzed postmortem. Another similar child was given 30mg./kg. of 2,3,5-triiodobenzoic for four days. The analyses are shown in table 2. In both cases the lung contained the largest concentration. Unfortunately no brain analyses were possible. Red and white cell counts which were done on the rabbits and on the children were not affected by the drugs.

Effect of B9 on the growth of the tubercle bacillus in the guinea pig: Perha ps one of the difficulties in studying the chemotherapy of tuberculosis has been the lack of a rapid method for testing the effect of a drug on the course of the disease. We have therefore devised a method based on the observations of Gardner (8, 9), Woodruff (10) and Woodruff and Kelly (11). They showed that when 0.1 to 0.5 mg. of tubercle bacilli are injected intraperitoneally a large number of tubercles appear in the omentum. According to Woodruff and Kelly these reach a maximum in twelve days after which they tend to break down and caseate. The events preceeding the tubercle formation have been worked out in detail by the latter authors. After an initial monocytic reaction immediately following the injection, the tubercle bacilli appear extracellularly in the omentum where they multiply rapidly during the third to seventh day. After this they are again engulfed in monocytes and tubercle formation occurs. It seemed to us that if a drug acts as a bacteriostatic, it would delay or prevent the multiplication of the bacteria during the third to seventh day and thus reduce the subsequent tubercle formation. Since this formation in the omentum is not accompanied by any marked haemorrhagic reactions, the weight of the omentum should be an index of the extent of tubercle formation. In the guinea pig, the omentum is attached to the greater curvature of the stomach and is readily removed quantitatively.

In order to use the omental weight as an index for the effect of a drug the following facts must be established. (*1*) *The weight of omentum in the normal guinea pig.* This is fairly constant if the weight is expressed in g./100 g. of pig. The average of 15 pigs was 0.21 g. of omentum per 100 g. and the individual values

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some weight loss toward the end of the experiment. The weight loss averaged 35 g. with doses up to 30 mg./kg. and with larger doses a loss of 80 to 100 g. occurred. Microscopical examination of the liver, kidney, intestine and brain of such animals showed no pathological changes in these organs. With B29 which is excreted much more rapidly no weight loss occurs up to 60 mg./kg. Two weeks after the administration of the B9 was stopped the guinea pigs regained their former weight.

varied from 0.16 to 0.28 g. The fat in the omentum accounts for most of this. (*2*) *The effect of injection of heat killed tubercle bacilli on the weight of the omentum.* Since tubercles can be formed in the omentum in response to the injection of lipid material alone, it is obvious that the increase in omental weight will depend on the number of bacteria injected, that is, the amount of lipoid. When 0.1 mg. of dead bacteria of our B_1 strain was injected the average weight of the omentum in 40 pigs was 0.25 g./100 g. with individual variations from 0.18 to 0.33 g. This increase over the weight of the control pigs is not significant but it indicates that a slight reaction is occurring. If 1.0 or 2.0 mg. of dead bacteria are injected the weight rises to 0.5 to 0.8 g. /100 g. The reaction of the omentum to the dead bacteria is a very important control, for tubercle formation is primarily a reaction of the animal to the organism. If a toxic drug is administered it may do two things: (*a*) decrease the reactivity of the tissues of the animal and thus decrease tubercle formation, and (*b*) decrease the fat content of the omentum. Both effects would decrease the weight of the omentum and give false positive results. These can be readily avoided by feeding the drug to pigs which have been injected with dead bacteria and comparing the weight of the omentum with untreated controls. (*3*) *The effect of the amount and virulence of the live tubercle bacilli on the weight of the omentum.* The following figures illustrate that when one culture is used the weight of the omentum increases with the amount of tubercle bacilli injected but that the increase is not proportional to the amount. Thus when 0.05, 0.1, 0.2 and 0.5 mg. of bacteria were injected the average weights were respectively 0.51, 0.61, 0.69 and 1.13 g./100 g. The reason for this lack of proportionality is not clear and it limits the quantitative interpretation of results obtained with a drug. Any given amount of bacteria may give varying results when cultures of different ages and virulence are compared. Thus, if a culture is subcultured every week instead of every three weeks the *in vitro* rate of growth is markedly increased and the injection of 0.1 mg. of such bacteria may give an omental weight of 1.0 g./100 g. which indicates an increase in virulence. On the other hand, our H37 strain which grows rapidly *in vitro* has a very low virulence and produces almost no omental reaction when 0.2 mg. is injected. It is obvious therefore that the weight of the omentum will vary from culture to culture, depending on the virulence of the bacteria, and that the weight must be determined for every culture used. We have found that for our drugs the best results are obtained when the omental weight averages 0.5 g./100 g. or about two and a half times the weight in the normal control pigs. If the degree or virulence of the bacteria is such that weights of 1.0 g./100 g. are obtained the drugs seem to have little or no effect. We interpret this as indicating that the infection is so overwhelming that the chemotherapeutic agent is powerless against it. The variations in omental weights, when a given amount of live culture is injected, is greater than when the dead culture is used. This is to be expected as individual guinea pigs vary in their susceptibility. The extent of the variations are shown in table 3 which illustrates a typical experiment. Table 3 also indicates another type of control that can be used. The 2,4,5-triiodobenzenesulfonic acid, as mentioned above, does not inhibit the growth *in vitro* in concentrations of 10 mg.

per cent. It presumably therefore would not inhibit growth *in vivo*. It was fed to infected guinea pigs in as high a concentration as B9. As table 3 shows, it has no effect on the weight of the omentum indicating that it does not interfere with the reaction of the body to the tubercle bacilli.

(*4*) *Miscellaneous:* The guinea pigs were usually killed twelve days after the inoculation. Variations of a day one way or the other did not affect the results. During this period occasional deaths from intercurrent infection occurred both in the control and treated groups. Occasionally a guinea pig had to be discarded when the evidence indicated that the bacteria were injected into the lumen of the

TABLE 3

The effect of different doses of B9 on the omental weights of guinea pigs

In experiment (a) 70 mg./kg. were administered daily for the first two days followed by 35 and 70 mg./kg. on alternate days. In (b) 60 mg./kg. were administered for the first two days followed by 30 and 60 mg./kg. on alternate days. In (c) 50 mg./kg. were administered for the first two days followed by 25 mg./kg. daily

CULTURE	DRUG	WEIGHT OF OMENTUM IN G./100 G.	AVERAGE	REMARKS
0.1 mg. live B_1.....	—	0.61, 0.34, 0.36, 0.33, 0.54, 0.84, 0.47, 0.48*	0.49	2 deaths
0.1 mg. heat killed B_1..	—	0.21, 0.17, 0.24, 0.22, 0.19, 0.25, 0.20, 0.24, 0.23, 0.22	0.22	
0.1 mg. live B_1.....	B9(a)	0.22, 0.25, 0.28, 0.19, 0.22, 0.39, 0.53, 0.20, 0.20	0.27	1 pig discarded because of very low omental weight
0.1 mg. heat killed B_1..	B9(a)	0.20, 0.18, 0.23, 0.20, 0.23, 0.15, 0.21, 0.25, 0.27, 0.38	0.23	
0.1 mg. live B_1.....	B9(b)	0.52, 0.25, 0.30, 0.46, 0.26, 0.47, 0.33, 0.33, 0.46, 0.30	0.37	
0.1 mg. live B_1.....	B9(c)	0.32, 0.38, 0.52, 0.48, 0.42, 0.43, 0.32, 0.46, 0.50, 0.43	0.42	
0.1 mg. live B_1.....	2,4,5-triiodobenzene sulfonic acid	0.51, 0.49, 0.65, 0.47, 0.26, 0.32, 0.50	0.46	1 death
0.1 mg. heat killed B_1..	2,4,5-triiodobenzene sulfonic acid	0.26, 0.20, 0.17, 0.16, 0.32, 0.32, 0.26, 0.32	0.25	

* This control series was chosen because it shows the widest variation.

intestine instead of intraperitoneally, or when the omental weight was a great deal below the average. The usual tests were performed with 10 guinea pigs each in the control group inoculated with live and dead bacteria and in similar treated groups. The guinea pigs were weighed before the injection and on the day they were killed. The latter figures were used for the calculation of the omental weights. The majority of the guinea pigs weighed between 400 and 600 g. and both sexes were used indiscriminately. The pigs were fed oats daily supplemented by cabbage and carrots twice a week.

Table 3 shows the effect of different doses of B9 and 50 mg./kg. of 2,4,5-triiodobenzenesulfonic acid on the omental weights in a typical experiment. Four

such experiments with B9 have been done with similar results. The drugs were fed twice a day at intervals of approximately twelve hours. At the end of twelve days the guinea pigs which were fed the largest concentration of B9 showed an average of a 65 g. weight loss. The sulfonic acid caused a 20 g. weight loss. The control experiment with dead bacteria showed that this weight loss with B9 had no effect on the omental weights. Table 3 shows that the highest concentration of B9 used inhibits tubercle formation in the omentum almost completely and that lower concentrations cause partial inhibition. If the amount or virulence of the live bacteria injected is increased so that the average control weights equal 1.0 g./100 g. of guinea pig the B9 treated animals show average weights of 0.8 g./100 g., that is, the drug is considerably less effective. B29 has no effect in reducing the omental weight.

DISCUSSION

The purpose of this paper is to call attention to a group of compounds that have marked effects in low concentrations on the metabolism and growth of the tubercle bacillus and to suggest a possible twelve-day test in guinea pigs. Whether positive results with such a test would be an indication of therapeutic action in human tuberculosis is impossible to say. B9 can be considered relatively nontoxic although it causes some weight loss in guinea pigs; 2,3,5-triiodobenzoic acid which gave negative results in the guinea pig test is tolerated in large doses by humans, so that it, as well as B9 may warrant a therapeutic trial in selected cases.

SUMMARY

1. The effects of a number of aromatic iodine compounds on the growth and metabolism of the tubercle bacillus have been studied.

2. A possible test in guinea pigs lasting twelve days has been outlined.

3. Using this test, the effect of certain of the iodine compounds has been described.

SUMARIO

1. Estúdianse los efectos de varios compuestos aromáticos de yodo, sobre la proliferación y metabolismo del bacilo tuberculoso.

2. Bosquéjase un ensayo en los cobayos que duró doce días.

3. Utilizándose dicho ensayo, se determinó el efecto de varios de los compuestos yodados.

Grateful acknowledgment is made for grants from the Ella Sachs Plotz Foundation and the Duke University Research Council to one of us (F. B.) and a grant from the Smith, Kline and French Laboratories to A. B. Our thanks are also due to Dr. Price Edwards, Dr. G. Margolis and Mr. W. H. Featherston for assistance in this work.

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CLINICAL AND LABORATORY NOTES

SIMULTANEOUS BILATERAL SPONTANEOUS PNEUMOTHORAX[1]

A Case Report

ANIBAL ROBERTO VALLE

Less than 100 cases of simultaneous bilateral spontaneous pneumothorax have been reported in the medical literature. The aetiological factors as given by Glickman and Schlomovitz (1) are as follows: tuberculosis, emphysema, pneumonoconiosis, bronchopneumonia, asthma, congenital cysts, tumors and interstitial fibrosis.

We present an additional case due to tuberculosis.

C. J., a thirty-year old, white, single male, shoeworker, was admitted to Koch Hospital, February 17, 1942 with a six-month history of bilateral chest pain pleuritic in type, fatigue, loss of weight, night sweats, anorexia, persistent nonproductive cough and ulceration of the tongue.

Previously, in 1934, he developed pleuritic pain, fatigue, cough and expectoration, haemoptysis and loss of weight. He was sent to Mt. St. Rose Sanatorium where the diagnosis of pulmonary tuberculosis was made and where he remained from May, 1936 to March, 1937 when he was discharged as arrested. After his discharge in 1937 he reported to his own physician for routine check-ups.

In August, 1940 he noticed the insidious onset of soreness at the base of his tongue on the right side. A biopsy of that lesion, made by Doctor Webb in November, 1940, showed tuberculosis. This lesion was treated by cauterization and ultraviolet radiation with some result.

Physical examination on admission revealed a well developed white male who did not seem acutely ill. Except for his chest pain and tongue soreness there were no other symptoms. Physical examination of his chest revealed signs of active tuberculosis in the upper half of each lung, both anteriorally and posterially. About every twenty-four hours he brought up a tablespoon of sputum which was positive for tuberculous bacilli both on direct smear and on concentration. The patient had a negative Kahn, a vital capacity of 1,900 cc., his urine was negative and the blood count was normal, except for the fact that it showed 12 staff cells and 11 lymphocytes. The patient was running a mouth temperature of 98° to 100° F.

An X-ray film of the chest, taken February 20, 1942, showed bilateral tuberculosis of the infiltrative type. He was diagnosed as F. A. II and kept on bed-rest.

On April 22, 1942, about eight weeks after admission, the patient had a sudden attack of dyspnoea and sharp pain on the right side. His pulse went up to 145 and examination of his chest showed a tympanitic note on percussion over the entire right side, tactile fremitus was absent and on auscultation breath sounds were very suppressed. Fluoroscopy showed a pneumothorax on the right; 450 cc. of air were removed. Before aspiration the manometer readings were −9 to +11 and after aspiration the readings were

[1] From the Robert Koch Hospital, Koch, Missouri, and the Washington University School of Medicine, St. Louis, Missouri.

−12 to −2. The patient was given one grain codeine hypodermically and immediate improvement was noted. The next morning the patient was dyspnoeic again and 1,500 cc. of air were removed from the right side with the manometer readings of −5 to +12 and −12 to −1. The patient was more comfortable.

On April 24, 1942, because the patient often became dyspnoeic, a continuous water-trap deflation set-up was arranged, with a catheter in the pleural space. Patient was given oxygen by means of a nasal catheter from this time until his demise. A portable X-ray film made at this time showed an increased pneumothorax on the right side (figure 1).

On May 9, 1942, in the morning, the patient was again very dyspnoeic and physical examination revealed a pneumothorax on the left side also, which was confirmed by a

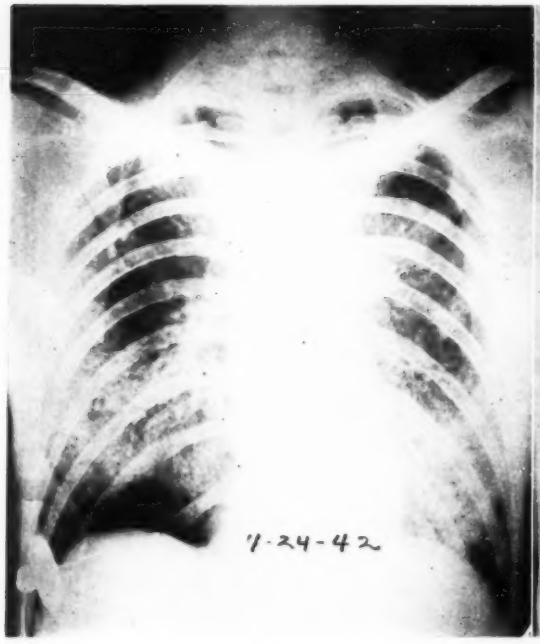

FIG. 1

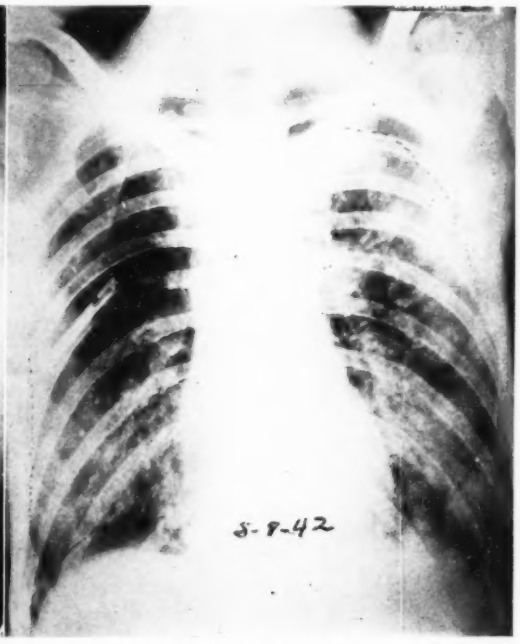

FIG. 2

portable X-ray film (figure 2). Six hundred cc. of air were removed from the left side with the manometer readings of +4 to −4 and −2 to −6. This procedure made the patient more comfortable. During the day the patient was very dyspnoeic again and 800 cc. of air were removed from the left side with manometer readings of −4 to +8 and −1 to −8. The water-trap was still connected to the right side at this time.

On May 9, 1942 at 9:25 p.m. the patient died.

The postmortem examination was performed on May 10 and revealed pneumothoraces on both sides. On examination of the gross specimen, we found several bronchopleural fistulae to be present in the right middle and lower lobes and in the left lower lobe. On sectioning it was found that the infiltrative tuberculous lesion extended to the periphery and in some sections the bronchopleural fistulae could be seen. With the exception of tuberculosis of the tongue and the chest findings, the autopsy findings were normal.

DISCUSSION

This is a case of simultaneous spontaneous bilateral pneumothorax with the main symptom of shortness of breath, due apparently to a very low vital capacity, 500 cc. The patient died seventeen days after the onset of the pneumothorax. It is worthy of note that in this case there are good reasons to believe that pulmonary tuberculosis was the cause of the bilateral spontaneous pneumothorax: sputum was positive in both direct smears and concentrations; biopsy of tongue ulcer showed tuberculosis; high temperature; pleuritic pain; and of foremost importance, the autopsy findings.

DISCUSION

Este es un caso de neumotórax espontáneo, simultáneo y bilateral, cuyo síntoma más llamativo es la disnea debida a la pequeña capacidad vital, 500 cc. El enfermo murió 17 días después del comienzo del neumotórax. Es digno de mención en este caso, que hay razones suficientes para creer que la causa del neumotórax espontáneo bilateral simultáneo fué tuberculosis: esputos positivos en examen directo y en concentraciones; la biopsia de la úlcera de la lengua fué positiva para tuberculosis; alta temperatura; dolores pleuríticos y sobre todo los hallazgos en la autopsia.

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ZIEHL-NEELSEN TECHNIQUE[1]

Staining Properties Modified by Different Preparations of Basic Fuchsin

DIRAN YEGIAN AND VERA BUDD

The red dye fuchsin was discovered by J. Natanson in 1856 and named in honor of the physician and botanist Leonhard Fuchs (1501–1556). The dye used in the Ziehl-Neelsen technique under the name of basic fuchsin is not a constant product, but is composed of an acetate or a chloride of rosaniline or pararosaniline. In a previous communication (1) it was shown that the staining properties of the acetate and chloride salts, at least so far as the tubercle bacillus is concerned, are quite different. Thus, films of tubercle bacilli prepared from virulent cultures or from pathological material presented from 50 per cent to 100 per cent of beaded microörganisms when the acetate salts were used in the Ziehl-Neelsen technique. On the other hand, with the chloride salts, the beaded bacilli were relatively few in number. Evidence was also submitted indicating that the beads do not represent spores as stated by Koch, nor are they, as suggested by subsequent observers, a reliable guide in determining differences in the age or the virulence of the microörganism. The beads presumably are in the nature of an artefact, since with a final washing of the stained preparation in 95 per cent ethyl alcohol, the beads are destroyed and the bacilli become solidly stained.

The difference in the staining properties of basic fuchsin indicated above prompted us to determine if possible which fuchsin salt would serve best for the demonstration of the tubercle bacillus.

MATERIALS AND METHODS

Four fuchsin dyes were studied: pararosaniline acetate, pararosaniline chloride, rosaniline acetate and rosaniline chloride,[2] which are found alone or in mixture in the commercial product "basic fuchsin." The dilutions of the dye are expressed in per cent, that is, the number of grams of dye dissolved in 100 cc. of 95 per cent ethyl alcohol.

The experiments, although made for the most part with cultures of virulent tubercle bacilli, were also made with bacilli present in pathological material and with nonpathogenic acid-fast bacilli. The cultures of bacilli to be stained were washed free of media and suspended in distilled water. With a platinum loop, the suspension was spread on a slide and allowed to dry at room temperature. The dye solution was then flooded on the slide and steamed gently for five minutes. After cooling for three to five minutes at room temperature, the dye was drained off and the slide thoroughly washed with water. The preparation was then decolorized with 5 per cent hydrochloric acid in 95 per cent ethyl alcohol

[1] From the New York State Hospital for Incipient Pulmonary Tuberculosis, Ray Brook, New York.

[2] More detailed and precise information on basic fuchsin can be gained by reference to H. J. Conn, Biological Stains, 1940.

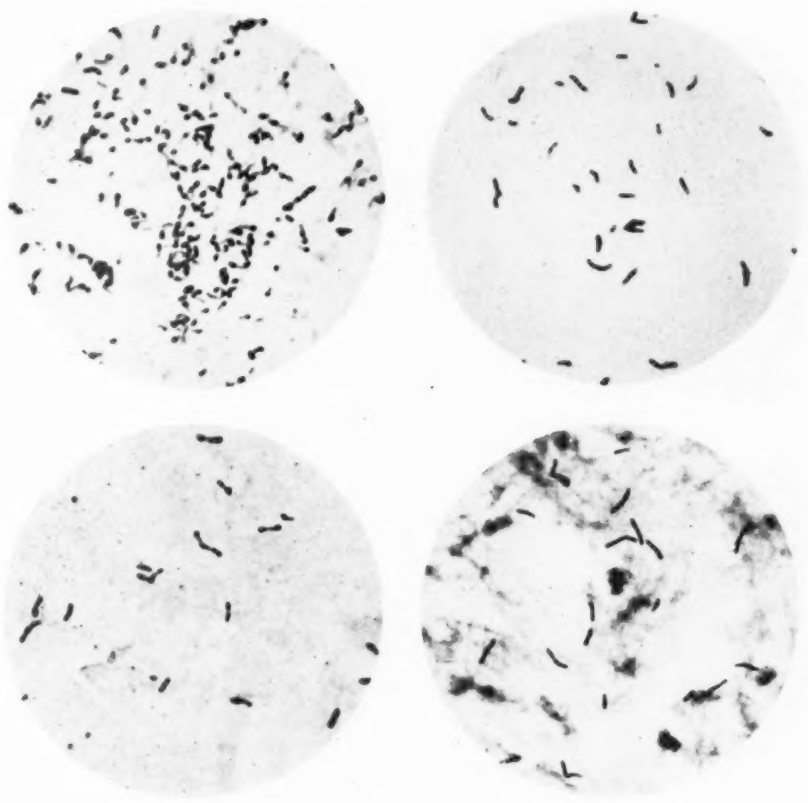

PLATE I

FIG. 1. (Upper left) Virulent culture of tubercle bacilli, stained with rosaniline acetate; tubercle bacilli beaded.

FIG. 2. (Upper right) Virulent culture of tubercle bacilli stained with rosaniline chloride; tubercle bacilli solidly stained.

FIG. 3. (Lower left) Tubercle bacilli in sputum stained with rosaniline acetate; tubercle bacilli beaded.

FIG. 4. (Lower right) Tubercle bacilli in sputum stained with rosaniline chloride; tubercle bacilli solidly stained.

for one and one-half minutes, washed with water and counterstained with brilliant green for thirty seconds. The solution of brilliant green used is prepared

TABLE 1

The effect of the preparation of basic fuchsin and the dilution of the dye on the beading of the tubercle bacillus

DYE USED	SOURCE	SOLUBILITY IN 95 PER CENT ALCOHOL	FINAL CONCENTRATION OF DYE	APPEARANCE OF STAINED TUBERCLE BACILLI
		per cent	*per cent*	
Pararosaniline acetate, Lot #8772	National Aniline Co.	13.0	1.3	50–90 per cent beads
			0.3	10–20 per cent beads
			0.14	No beads; bacilli not distinct
Pararosaniline acetate, Lot #6820	National Aniline Co.	11.42	1.142	50–100 per cent beads
			0.5	50 per cent beads
			0.3	10–30 per cent beads
			0.14	No beads; bacilli faintly stained
Pararosaniline acetate, no lot number	Coleman & Bell	7.42	0.742	50–80 per cent beads
			0.5	50 per cent or more beads
			0.3	20–30 per cent beads
			0.14	No beads, many bacilli indistinct
Basic fuchsin, NF 31, pararosaniline acetate	National Aniline Co.	9.45	0.945	60–70 per cent beads
			0.5	40–50 per cent beads
			0.3	10–20 per cent beads
			0.15	Few beads, small, not distinct
Pararosaniline chloride Lot #9155	National Aniline Co.	6.87	0.687	Occ. 5–10 per cent beads
			0.3	No beads; bacilli solidly stained
			0.14	No beads; few bacilli, faintly stained
Basic fuchsin, rosaniline chloride, Lot #391205	Coleman & Bell	6.07	0.607	60–70 per cent beads, sometimes less
			0.3	No beads; bacilli solidly stained
			0.15	No beads; few bacilli, faintly stained
Basic fuchsin, rosaniline chloride, C.E. 16	Coleman & Bell	5.21	0.521	Some preparations show 2–5 per cent beads
			0.3	No beads; bacilli solidly stained
			0.5	No beads, bacilli solidly stained
			0.15	No beads; few bacilli, faintly stained
Pararosaniline chloride, no lot number	Coleman & Bell	5.06	0.506	Some preparations show 2–5 per cent beads
			0.5	No beads; bacilli solidly stained
			0.3	No beads; bacilli solidly stained

as follows: Dissolve 1 g. brilliant green in 997.5 cc. of distilled water and add 2.5 cc. of 4 per cent sodium hydroxide.

In other experiments, the technique was modified as follows: the staining was

carried out at 90°C. for twenty minutes, at 37°C. for two hours and at 20°C. and 10°C. for twenty-four hours, and the decolorizing agents used were 3 per cent hydrochloric acid, 2.5 per cent nitric acid and 5 per cent sulphuric acid in 95 per cent ethyl alcohol. These alterations in technique did not affect the results appreciably.

It was found that the composition of the dye used in the Ziehl-Neelsen technique markedly affected the appearance of the tubercle bacillus. Thus, films of tubercle bacilli prepared from virulent or avirulent cultures and from pathological material show from 50 per cent to 100 per cent of beaded microörganisms when the commonly used saturated solution of rosaniline or pararosaniline acetate is employed in the Ziehl-Neelsen technique. In color, the beads are a deep red, or even dark purple, they may number from 1 to 5 and their diameter slightly exceeds that of the acid-fast rod (see plate). The beaded forms are decreased in number or may be absent when weaker solutions of this dye are used, but here the bacilli are very faintly stained and difficult to identify. Table 1 gives the name of the dye, the number of the sample, the dilution of the dye used in the Ziehl-Neelsen technique and the per cent of the beaded forms of the bacilli. The beaded bacilli may be readily mistaken for cocci, particularly when the material to be examined contains only a few bacilli. Therefore, in the Ziehl-Neelsen technique, the acetate salts should not be selected for the demonstration of the tubercle bacillus, at least for purposes of diagnosis.

On the other hand, when rosaniline and pararosaniline chloride in saturated solutions are used in the Ziehl-Neelsen technique, the beaded microörganisms are relatively few in number. Further experiments show that, when the chloride salts are used in a final concentration of 0.3 per cent instead of the usual higher concentrations, the beaded forms do not appear, and all the bacilli without exception are solidly stained and easily recognized. We therefore recommend that the chloride salts in a final concentration of 0.3 per cent be employed in the Ziehl-Neelsen technique.

The term "basic fuchsin" includes several salts with different staining properties and this has been a source of confusion in the study and identification of the tubercle bacillus. It would seem advisable, therefore, that the term "basic fuchsin" be discontinued and that the label give the exact composition of the fuchsin dye: for example, "Rosaniline Chloride."

REFERENCE

(1) YEGIAN AND BAISDEN: Factors affecting the beading of the tubercle bacillus stained by the Ziehl-Neelsen technique, J. Bact., 1942, *44*, 667.

STATISTICAL DATA

Edited by MARY DEMPSEY

NEW CASES OF TUBERCULOSIS DISCOVERED BY CASE-FINDING SURVEYS

For years and years the program of tuberculosis prevention and control in this country has been seriously handicapped by the difficulty in locating large numbers of cases early enough to eliminate the spread of infection and to effect cures in the majority of instances. The Early Diagnosis Campaign, promoted each spring by tuberculosis associations, represents an educational effort to encourage case-finding while patients are still in the early stages of the disease. In the past, this campaign has resulted in numerous case-finding surveys among students, teachers, nurses, patients in mental hospitals, industrial workers and various other special groups. In spite of all this activity the proportion of minimal cases admitted to sanatoria has remained discouragingly small.

Since the beginning of the war, however, case-finding has been undertaken on a stupendous scale never before visualized. Authoritative information indicates that the armed forces will include nearly eleven million men by the end of 1943. Except for several hundred thousand inducted in the very earliest days of the war emergency all these men will have been X-rayed.

Before 11,000,000 men can be accepted by the military and naval forces, probably 16,000,000 or 17,000,000 will have to be examined. As time goes on, the proportion of those examined who are accepted as recruits will undoubtedly become lower and lower. No information is available as to the number of X-ray films made of those men rejected by local boards for obvious causes, such as gross mental defects, blindness, amputations, etc., but presumably the number is small. For this reason it seems wise to assume that at least 12,000,000 men will have been X-rayed by the end of 1943 in connection with examination for the armed forces.

The U. S. Public Health Service is simultaneously carrying on an intensive case-finding campaign among employees of certain war plants, as well as those in government departments. The Service estimates that approximately 2,000,000 of these war workers will have been X-rayed by the end of this year. This activity is supplemented by similar campaigns which are being conducted in many states and cities.

Careful estimates based on actual findings to date indicate that by the end of this year approximately 25,000 persons will have been diagnosed as in need of hospitalization who in ordinary times would not have been suspected of having tuberculosis. The chief reason for this statement is the fact that a majority of the newly found active cases are ostensibly asymptomatic. We are reliably informed that probably only a small proportion of them have a history of contact; as a result, relatively few would ever have been examined previously at a clinic.

A detailed account of the method used in arriving at this estimate of 25,000

newly discovered cases is given on pages 62 and 63; undoubtedly the estimate errs on the side of understatement.

X-ray examinations given millions of men at induction stations, together with similar examinations of more than 2,000,000 employees in war plants, will have resulted in the discovery of 45,000 to 50,000 cases with *significant tuberculous lesions*, according to the best estimate available. Of this number, competent diagnosticians judge that at least 30,000 persons who are in need of sanatorium care will have been discovered before the end of the year.

In certain areas where the public health program is unusually well developed sample tests have been made to ascertain what proportion of the deferred draft registrants with active tuberculosis are already known to the proper health authorities. These tests indicate that only 10 to 16 per cent of such active cases had previously been reported to the health departments. Among industrial employees only 5 per cent of the active cases found were known to the health officials.

In general, the X-raying of workers in war plants has led to the discovery of a larger proportion of significant cases than were found among drafted men, since workers of both sexes and all ages are being examined in these plants. This industrial campaign was inaugurated so recently that it has not yet proved possible to analyze the results in as much detail as in the case of men examined for the armed forces.

The fact that these case-finding surveys are discovering so many new cases needing hospitalization calls for immediate and practical action. For the first time in the history of the tuberculosis program it has become possible to carry on the campaign on a different plane than was ever feasible heretofore.

This estimate points out the need for greatly increased sanatorium facilities. Even before the war such facilities were considered adequate in but few states. Now, if tuberculosis workers are to do their part in counteracting the generally accepted tendency of tuberculosis to become more prevalent in war times, they must embark on an intensive campaign for more hospital beds and better hospital facilities. Obviously this campaign is needed much more urgently in some states than in others.

In the past the ratio[1] of two beds per annual death has been accepted as the *minimum* standard used in determining the adequacy of hospital facilities. Such facilities have been considered definitely inadequate in those states with fewer than two beds per annual death. Similarly, it has been customary in the past to base the ratio of hospital beds per annual death on the number of beds provided for tuberculous patients in sanatoria and in hospitals with tuberculosis departments. This generally accepted method made no allowance for beds provided to care for tuberculous inmates of mental and penal institutions; neither has it allowed for facilities in federal hospitals. For the purpose of this analysis, however, it seems wise to include beds in mental and penal institutions when computing this ratio.

[1] In computing these ratios, beds in federal hospitals are not included because they are not restricted to the residents of the state in question.

Comparing the number of deaths in 1941 with all available beds except those in federal hospitals,[1] we find that only 15 states and the District of Columbia meet this minimum standard, while 11 states failed to reach the level of even one bed per annual death.

The *recommended* standard as opposed to the *minimum* standard is three beds per annual death. Based on 1941 deaths, 7 states and the District of Columbia met this standard in 1942. They were Colorado, Connecticut, Michigan, Minnesota, North Dakota, Rhode Island and Wisconsin.

Now that case-finding surveys are being made on a nation-wide scale never before contemplated, it is obvious that facilities must be provided to care for those diagnosed cases in need of treatment which are being found in an earlier stage than was ever before possible. With this information in hand it is the responsibility of the health departments and of tuberculosis associations to meet the need.

In order to determine what responsibility for increased hospital facilities each state must accept, the 25,000 additional new cases estimated to be in need of hospital care have been prorated in accordance with the distribution of tuberculosis deaths in 1941. For example, in that year 5 per cent of all tuberculosis deaths in the United States occurred in Ohio. Therefore, we may assume that 1,250 of these 25,000 estimated new cases will prove to be Ohio's responsibility. On a minimum basis of two beds per death in 1941, Ohio should have 5,922 beds. In 1942, however, the state had but 4,960 nonfederal beds,[2] or a deficit of 962 beds, even based on a minimum standard. With an estimated figure for Ohio of 1,250 new cases, which under normal conditions would not have become known at this time, it becomes evident that Ohio should have approximately 2,200 additional beds if it is to provide care for all newly found cases in need of hospitalization. Evidence that this figure is not exorbitant is provided by the fact that, even with 2,200 additional beds, Ohio would still be short the recommended three-bed ratio by about 1,700 beds.

The case of Minnesota is somewhat different. This state, with more than three beds per annual death, has more than enough facilities to meet the minimum standard and still can provide for its expected quota of approximately 300 new cases found among men examined for the armed forces and in industrial plants.

It is one thing to work for additional beds in peace times with the knowledge that such beds are required as new cases are found in the ordinary course of events. Now, however, during this war period those in charge of the tuberculosis program are faced with a much greater urgency. By the end of this year approximately 25,000 cases will have been diagnosed as in need of hospitalization, many of which would not otherwise have been known until some time later. If we expect to reduce tuberculosis to a minimum at any time in the near future, then the necessary beds must be provided for these patients.

This campaign, to be effective, will necessarily prove strenuous. For some time past, sanatoria have been closing wards and curtailing activities because of the difficulty in obtaining adequate medical, nursing and domestic personnel. The mere effort to keep these hospitals going in accordance with acceptable standards represents a serious undertaking. When to this is added the urgent need for greatly increased facilities, the responsibility becomes indeed stupendous.

Some persons may argue that additional hospital facilities on such a large scale will not be needed in view of the fact that the tuberculosis death rate in the

[1] See footnote 1 on page 59.

[2] Including beds for tuberculous patients in mental and penal institutions.

country as a whole declined 35 per cent during the past decade. We have no assurance, however, that this decline will continue year after year, especially if the war with all its concomitant strain should last for two or three years more. Since 32 states need from 100 to 6,000 additional beds each to care for their share of this problem, it seems imperative that these states initiate a determined campaign to provide adequate facilities in the very near future.

As Sir Arthur S. McNalty, the distinguished British physician, has so aptly said, "Tuberculosis is one of the camp followers of war."

Analysis of Additional Hospital Facilities Needed for Tuberculous Patients, by State: 1943

STATE	TUBERCULOSIS DEATHS IN 1941	NON-FEDERAL BEDS[1] IN 1942	BEDS NEEDED TO MEET MINIMUM STANDARD OF TWO PER ANNUAL DEATH	EXCESS OR DEFICIT WITH REFERENCE TO MINIMUM STANDARD	ESTIMATED NUMBER OF NEW CASES NEEDING HOSPITALIZATION	TOTAL NUMBER OF ADDITIONAL BEDS NEEDED
Alabama	1,474	662	2,948	−2,286	622	2,908
Arizona	850	660	1,700	−1,040	359	1,399
Arkansas	956	1,401	1,912	−511	403	914
California	3,751	8,515	7,502	+1,013	1,583	570
Colorado	550	1,811	1,100	+711	232	—
Connecticut	587	2,113	1,174	+939	248	—
Delaware	153	266	306	−40	65	105
District of Columbia	439	1,347	878	+469	185	—
Florida	911	981	1,822	−841	384	1,225
Georgia	1,384	1,823	2,768	−945	584	1,529
Idaho	83	43	166	−123	35	158
Illinois	3,484	6,243	6,968	−725	1,470	2,195
Indiana	1,319	1,962	2,638	−676	557	1,233
Iowa	386	1,039	772	+267	163	—
Kansas	404	682	808	−126	170	296
Kentucky	1,954	1,132	3,908	−2,776	824	3,600
Louisiana	1,318	959	2,636	−1,677	556	2,233
Maine	254	584	508	+76	107	31
Maryland	1,358	1,999	2,716	−717	573	1,290
Massachusetts	1,656	4,591[2]	3,312	+1,279	699	—
Michigan	1,739	5,564	3,478	+2,086	734	—
Minnesota	754	2,527	1,508	+1,019	318	—
Mississippi	999	754	1,998	−1,244	422	1,666
Missouri	1,737	2,558	3,474	−916	733	1,649
Montana	203	272	406	−134	86	220
Nebraska	202	387	404	−17	85	102
Nevada	62	12	124	−112	26	138
New Hampshire	137	240	274	−34	58	92
New Jersey	1,803	4,903	3,606	+1,297	761	—
New Mexico	385	432	770	−338	162	500
New York	6,236	15,405	12,472	+2,933	2,631	—
North Carolina	1,757	2,229	3,514	−1,285	741	2,026
North Dakota	117	459	234	+225	49	—
Ohio	2,961	4,960	5,922	−962	1,249	2,211
Oklahoma	1,043	907[2]	2,086	−1,179	440	1,619
Oregon	282	736	564	+172	119	—
Pennsylvania	4,083	7,269	8,166	−897	1,723	2,620
Rhode Island	269	854	538	+316	114	—
South Carolina	839	1,147	1,678	−531	354	885
South Dakota	178	262	356	−94	75	169
Tennessee	2,328	1,490	4,656	−3,166	982	4,148
Texas	3,684	2,927	7,368	−4,441	1,554	5,995
Utah	66	112	132	−20	28	48
Vermont	129	182	258	−76	54	130
Virginia	1,639	2,078	3,278	−1,200	692	1,892
Washington	701	1,401	1,402	−1	296	297
West Virginia	830	1,334	1,660	−326	350	676
Wisconsin	781	2,404	1,562	+842	330	—
Wyoming	36	33	72	−39	15	54

[1] Includes beds set aside for tuberculous patients in mental and penal institutions.

[2] This figure represents an understatement because one ward in a prison is set aside for tuberculous prisoners. The number of beds is not reported.

Methods used in estimating that 25,000 previously unknown cases of tuberculosis which need immediate hospitalization will have been discovered before the end of 1943.

Case-finding among Drafted Men and Those Who Tried to Enlist

Total number expected to be in the armed forces by the end of 1943	11,000,000
Estimated number of men called for examination	16,000,000
Estimated number given X-ray examinations before induction	12,000,000
At least 1 per cent deferred for tuberculous conditions, including active and arrested cases, those with calcifications, etc.	120,000
One-third of those deferred are classified as having lesions considered significant	40,000
One-half of the significant cases are classified as moderately advanced and far advanced, all of which need sanatorium care	20,000
One-fourth of the remainder of the significant cases, classified as minimal, are considered to be in need of sanatorium care	5,000
Total number of cases found among recruits who are in need of sanatorium care	25,000
After checking a representative sample of these 25,000 cases to health department reports, 87 per cent were found to be unknown	21,750

Case-finding among Industrial Employees

Total number to be given X-ray examinations by the end of 1943	2,000,000
One and one-half per cent will have been found to have tuberculosis	30,000
One-third of these 30,000 will have been classified as having active tuberculosis	10,000
Industrial workers with active tuberculosis who are considered to be in need of sanatorium care	6,000

After checking a representative sample of these 6,000 cases to

health department reports, 95 per cent were found to be unknown	5,700
Total number of cases found to have significant lesions which need hospital care and which were previously unknown	27,450
Discounting this figure approximately 10 per cent, the accepted estimate in round numbers is	25,000